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Review and Meta-analysis

Bioactive Peptides: A Complementary Approach for Cancer Therapy

Nazanin Khademi — Master's Degree in Midwifery Consultation, School of Nursing and Midwifery, Hamadan University of Medical Sciences, Iran.
Nariman Mehrnia — University of Medical Sciences, Iran.
Mojtaba Esmailpour Roshan — Islamic Azad University of Garmsar, Garmsar, Iran.

Background: The relentless pursuit of effective cancer treatments has led researchers to explore bioactive peptides as a complementary approach to cancer therapy. These peptides, which can be of natural or synthetic origin, are not only identified as potent therapeutic agents but also exhibit significant diagnostic capabilities. The review aims to summarize the properties, classification, and mechanisms of action of these natural peptides on different cancer cell lines, suggesting their potential as safer and more effective cancer treatments.

Objective: To provide an in-depth exploration of bioactive peptides derived from natural sources, revealing their anticancer properties and theoretical models that explain their actions. The review also addresses the complexities of ACP production and classification and sheds light on their potential as less harmful and more precise alternatives to conventional cancer therapies.

Method: The review includes a comprehensive analysis of the literature on bioactive peptides, focusing on their origin, properties, classification, and mechanisms of action. It examines various theories that explain the effect of bioactive peptides on cancer cells and discusses the natural sources of these peptides, their production processes, and classification into different types of ACPs.

Findings: The review identifies a range of bioactive peptides with anticancer properties from various sources, including animals, plants, fungi, and marine organisms. These peptides act through diverse mechanisms, such as membrane disruption, apoptosis induction, and immune system modulation. The review provides a detailed account of the peptides' effects on different cancer cell lines and their potential therapeutic applications.

Discussion and Conclusion: The review concludes that bioactive peptides offer a promising avenue for cancer therapy, with the potential to revolutionize treatment landscapes. It emphasizes the need for further research to fully realize the therapeutic potential of these peptides and their role in the future of cancer treatment. The review also highlights the importance of understanding the structure-function relationship of bioactive peptides to enhance their therapeutic efficacy and reduce systemic toxicity.

Introduction

As one of the leading causes of morbidity and death, cancer poses a serious danger to human health and wellbeing worldwide. About 20 million deaths were linked to cancer according to a World Health Organization report [1-3]. Men were more likely to die from lung, prostate, colorectal and stomach cancers while women were more likely to die from breast, colorectal, lung, cervical and thyroid cancers. Currently, the gold standard for cancer treatment consists of three main components: radiation therapy, chemotherapy, and surgery [4]. However, the conventional approach has some drawbacks such as the lack of screening tools for early cancer identification

and the lack of specialized drug delivery methods for particular tumor types. Moreover, most standard anticancer medications lack the ability to differentiate between healthy and malignant cells which can lead to unwanted side effects and systemic toxicity [5]. Given the aforementioned difficulties, the need for therapeutic medications that specifically target cancer is paramount. Bioactive peptides are gaining a lot of interest in this regard as potentially effective therapeutic agents for the treatment of cancer [6]. People who have been diagnosed with cancer in recent decades have demonstrated an increasing interest in adding complementary medicine (CM) to their treatment plan. The aim of Anticancer peptides is that the general health and well-being are to be improved, traditional cancer treatments to be more successful, survival rates to be raised and side effects related to the disease and treatments to be reduced [7]. A branch of supplementary medicine that uses organic materials namely bioactive peptides is one such category. These peptides are characterized as brief sequences of amino acids (3–20 AAs) that are present in proteins and have favorable effects on the regulation and control of metabolic processes. They can also be considered as useful approach in the treatment and prophylaxis of many illnesses [8]. Bioactive peptides are latent within parent proteins and can only be released through enzymatic hydrolysis, food processing or microbial fermentations to exhibit their beneficial effects. These peptides have the potential to be exploited in the management and prevention of diseases. Many of the body's normal functions are triggered or regulated by the interaction of particular amino acid sequences that appear as peptides or protein fragments suggesting that these could be employed in a broad spectrum of therapeutic interventions [9]. The relationship between the structure and functions of bioactive peptides has not yet been fully established so this study's focus is on the most recent studies on the immunomodulatory and anticancer effects of bioactive peptides derived from natural sources using enzymatic hydrolysis. It has been discovered that these peptides cause apoptosis or programmed cell death in malignant cells and prevent the growth and multiplication of different cancer cells. These bioactive peptides can also affect the immune system demonstrating actions that are they have both stimulatory and anti-inflammatory property. Because of these characteristics, bioactive peptides are attractive candidates for the creation of novel functional and therapeutic dietary additives. Peptides are intriguing and hopeful therapy possibilities because of their favorable characteristics which includes their decreased toxicity when compared to conventional chemical medications and their high affinity and specificity for target molecules so there is a possibility to employ these peptides in place of traditional medications [10, 11]. Membrane separation techniques, ultrafiltration, membrane chromatography and ion exchange protocols are the main methods used in the production and purification of bioactive peptides. Furthermore, while certain bioactive peptides like endorphins are created naturally while others are made by enzymatic cleavage, microbial fermentation and protein breakdown. Usually, bioactive peptides have a molecular weight of roughly 102–103 Da and comprises of 2–50 amino acid residues. As a result, they can easily break through or breach the cell membrane causing necrosis or apoptosis. Despite the advancements and successes in the detection and treatment of cancer, novel strategies in particular the use of natural peptides have been investigated for development of more potent alternatives for cancer treatment [12]. Many bioactive peptides with anti-inflammatory, anti-hypertensive, antimicrobial and anti-cancer properties have been discovered and isolated from natural animal and plant sources with the advancement of biology and biomedicine [13].

Cancer is a general term for a variety of diseases that have harmful effects such as uncontrolled cell division leading to the formation of a cell cluster that can invade nearby tissues and dispersing to other regions by a process known as metastasis [14]. Thus, there is an incredible need for the development and application of a novel therapeutic agent. Against the backdrop of traditional cancer treatment modalities like radiotherapy, chemotherapy or surgery as well as optical methods like CT, MRI and PET for diagnostic and therapeutic applications, bioactive molecules, especially anticancer peptides are extremely important in this field. Naturally occurring peptides possess a wide range of amino acid residues (5 to 50) and are notable for their minute size, high activity, low immunogenicity, excellent biocompatibility, diversity of sequence, and multiple modification sites for functional molecules. These attributes make peptides extremely promising especially in the field of cancer therapy [15]. Antimicrobial Peptides (AMPs) are amphiphilic peptides that are created by

the immune system and are derived from a wide range of species. They are the first line of defense against invasive infections and are encoded with genes. Amphiphilic peptides have attracted a lot of attention for their potential therapeutic applications because of their wide range of activity and little likelihood of causing resistance.

2. Membrane-active and Non-active Peptides

Although the exact nature of AMPs' anticancer action in respect to malignant targets is yet unknown, evidence points to a major involvement for pathways involving both membrane-lytic and non-membrane- lytic activity. Pentostatin and Properdistatin are two examples of membrane-inactive peptides that have been identified as having non-damaging membrane processes [16]. Two prime examples of such processes are the inhibition of angiogenesis and the activation of extrinsic apoptotic pathways [17]. Membrane-active peptides with selectivity for bacterial cell membranes include Defensins, Cecropins, and Magainins which are examples of antimicrobial peptides. Antimicrobials are categorized into different groups based on their structural features including AMPs rich in cysteines, β-sheet AMPs (α-defensins and β-defensins) and AMPs with α-helices (LL-37 Cathelicidin, Cecropins, and Magainins). AMPs with extended confirmation are high in histidine, arginine, proline, glycine, and/or tryptophan and peptide loops have a single disulfide link (Bactenecin). Many of the antimicrobial peptides (AMPs) are amphipathic in non-polar solvents and contain positive charges. Through electrostatic interactions, they cling to the negatively charged cell membranes of bacteria disrupting their functions and ultimately causing these single-celled organisms to perish. These pore-forming peptides attack the membranes of cancer cells and can cause necrosis or apoptosis which results in the death of cells [18, 19]. Antimicrobial peptides or AMPs not only cause disruption of the mitochondrial membrane during programmed cell death (apoptosis) but also assault negatively-charged molecules on the malignant surface of cells which causes breakdown of cells thereby leading to necrosis-induced cell death. In addition to AMPs, other venom-like peptides that lyse bacterial and eukaryotic cell membranes have also been discovered including Melittin and Masteroplans [20-23].

2.1 Mechanism of action of membrane active biopeptides for anticancer activity

The target membrane and the peptide's properties determine the mechanism underlying the membrane disruption or membranolytic activity of bioactive peptides which in turn affects the peptides toxicity and selectivity. There are various ways in which membrane rupture can happen which includes pore formation in the lipid (barrel-stave and toroidal pore models), thinning of the membrane bilayer and dissolution (carpet model) and apoptosis or cell death via the mitochondrial pathway are illustrated below [24]:

2.1.1. The barrel-stave model

This model explains how peptides diffuse and enter the lipid bilayer of a membrane by organising themselves into helices which create channels that stretch and span the membrane. Several well-known bioactive peptides such as Melittin (from the European honey bee), Pardaxin (from the Red Sea sole), Cecropins (from moths) and Magainins (from frogs) promote cell lysis via pore formation.

2.1.2. Toroidal model

In this model, the pore wall is formed by lipid head groups and bioactive peptide are aligned parallel to the membrane and a water pore is positioned centrally. Magainins (derived from bee venom), Melittin (from frogs) and Protegrins (from porcine leukocytes) follow this mechanism of

action.

2.1.3. Carpet model

The “carpet” model describes how peptides attach themselves parallel to the membrane surface without creating pores, yielding a model like a carpet when combined with more peptide monomers. Micelles are created when the membrane is disrupted and at a specific peptide concentration, the membrane structure is damaged in a way similar to that of detergents.

2.1.4. Apoptosis or cell death via the mitochondrial pathway

Some bioactive anticancer peptides cause apoptosis or cell death via the mitochondrial pathway in addition to causing cell death through disruption of the plasma membrane. The mechanism of necrosis is the early opening of the inner mitochondrial membrane (IMM) and formation of mitochondrial permeability transition pore (mPTP) which stops ATP synthesis. This allows a lot of water and other small solutes to enter the mitochondrial matrix through electrochemical gradients causing severe osmotic swelling in the mitochondria which leads to necrotic death. Additionally, certain pro- apoptotic substances are released during mitochondrial outer membrane permeabilization (MOMP) including endonucleases, second mitochondria-derived activator of caspase (Smac), cytochrome c (Cyt c) which activates caspases and apoptosis-inducing factor (AIF). In breast cancer cells, the antimicrobial peptides NRC-03 and NRC- 07 from the Atlantic flounder target results in mitochondrial damage and a induces a loss of transmembrane potential. In addition, the peptide inhibits the synthesis of DNA or promotes the generation of reactive oxygen species (ROS) and apoptosis via mitochondrial-dependent apoptosis. The Japanese sea hares urilide specifically binds to prohibition 1 (PHB1) in the inner membrane of mitochondria, initiating the proteolytic processing of ocular atrophy1 (OPA1) and causing apoptosis that is triggered by the mitochondria induced apoptosis. Additionally, it prolongs mitochondrial fragmentation by boosting OPA1 processing which results in the loss of membrane potential and induce apoptosis. Goat spleen-derived ACBP inhibits the cell cycle and reduces the expression of the genes c-myc, cyclin D1, bcl-2 and PCNA hence inducing apoptosis. Additionally, it raises the expression of p27Kip1, p21Waf1 and p16Ink4. By altering the PARP-p53-Mcl-1 signalling pathway, ACBPs also prevent the development of human colorectal cancer cells and cause apoptosis.

3. Natural Bioactive Peptides with Anticancer Activity

Active peptides have gained significant attention because of the praiseworthy benefits they have on human health. Because of their small size, lesser toxicity, higher permeability and capacity to diffuse across cells active peptides have several advantages as an alternative medication. One such benefit is their ability to deeply permeate tissues. Table 1 below lists bioactive peptides with anticancer properties from several sources.

Source	Peptides	Mechanism	Cancer type	Cancer cell line	References
Goat spleens or livers	ACPB	Inhibits HCT116 cell growth, enhances UV-induced apoptosis, enhances the expression levels of PARP and p53 and suppresses the expression of Mcl-1	Human colorectal tumor cell line	HCT116, GCSCs, BGC-823 and CD44+ cells	[25, 26]
Cyanobacteria/	Apratoxin A	Inhibition of Cell	Cervical cancer	HeLa	[27]

Lyngbya boulloni		cycle			
Frog/Litoria aurea and Litoria raniformis	Aurein 1.2	Interaction with lipid membrane of T98 G cells	Glioblastoma multiforme	T98 G cells	[28-30]
Marine/ Japanese sea hare Dollabella auricularia, marine cyanobacterium, Lyngbya majuscula	Aurilide	Mitochondria-induced apoptosis	NA	NCI-H460 human lung tumour, the neuro-2a mouse neuroblastoma, leukaemia, renal, and prostate cancer cell lines	[31]
Fungi/ Fusarium sp.	Beauvericin	Growth inhibition, apoptosis induction via mitochondrial pathway	Human epidermoid carcinoma	KB	[32]
Cyanobacteria / Nostoc linckia and Streptomyces griseus	Borophycin	Cytotoxicity	Epidermoid carcinoma and human colorectal adenocarcinoma	LoVo and KB	[33, 34]
Bovine/Bos Taurus	Bovin Lactoferricin	Induce apoptosis	Leukemic and neuroblastoma cell	Meth A	[35]
Limnonectes fujianensis	Brevinin	Penetrating into the lipidic bilayer causing death of cells	Lung cancer, melanoma cell, glioblastoma, colon cancer cell	U251MG, HCT116, MDA-MB-231, SW480, A549, H460, SMMC7721, B16-F10	[36]
Rana ridibunda	Brevinin 2R	Lysosomal death and autophagy-like cell death	Breast adenocarcinoma, and lung carcinoma cell	HeLa, MCF-7, A549	[37]
Bufo bufo gargarizans	Buforin IIb	Mitochondrial apoptosis	Leukaemia, breast, prostate, and colon cancer	hepG2MCF-7, MDA-MB-231, PC-3, DU145	[38]
Goat/Capra hircus	ChMAP-28	Cytotoxic activity	NA	HL-60, A431, SKBR-3, HEK 293 T, HEF, NHA	[39]
Larvae of Bombyx mori	CecropinXJ	Growth Inhibition	Bladder cancer, HCC, gastric carcinoma, fibrosarcoma and leukaemia cells	Huh-7	[40]
Fungus/ Acremonium persicinum	Cordyheptapeptide	Cytotoxic activity	Oral human epidermoid carcinoma, breast cancer, and small cell lung cancer	SF-268, MCF-7, and NCI-H460 tumour cell lines	[41, 42]
Cyanobacteria/ Spirulina platensis (C-phycocyanin by cyanobacteria)	C-phycocyanin (C-PC)	Apoptosis induction	NA	HeLa cells	[33]
Cyanobacteria/ Nostoc sp. ATCC 53789 and Nostoc sp. GSV 224	Cryptophycin-52	Disruption of tubulin-dynamics	Drug-resistant murine and human solid tumours	Human tumour cell lines	[43]
Cyanobacteria / Lyngbya majuscula	Curacin A	Inhibition of tubulin polymerization by binding at colchicine site	NA	Leukemic cell L1210	[44]
Wasp/Oreumenes decoratus (wasp venom)	Decoralin (Dec-NH2)	Decoralin is an α-helical peptide that cause necrosis of MCF-7 cells	Breast cancer	MCF-7	[45]
Humans/ Homo sapiens	α-Defensins	Cytolytic activity	Human myeloid leukaemia cell line	U937, HCT-116, MCF-7, A549, PC-3,	[46]

				HeLa	
Humans/ Homo sapiens	β-Defensin-3	Binding to cell membrane causing cytolysis	Several cancers	HCT-116, MCF-7, A549, PC-3, HeLa, U937	[47]
Frog/Pithecopus (Phyllomedusa) hypochondrialis	Dermaseptin- PH	Cell membrane permeability disruption	Several cancers	MCF-7, H157,U251MG, MDA-MB- 435S, and PC-3	[48]
Cyanobacteria/ Lyngbya majuscula	Desmethoxymajusculamide C (DMMC)	Actin depolymerization	Human colon	HCT-116	[49]
Ascidian Diazona chinensis	Diazonamide A	Inhibition of Tubulin Polymerization, Blocking of cell division	Human tumor cell, human cervical carcinoma, osteosarcoma cells	HeLa cell	[50]
Cyanobacteria/ Phormidium tenue	Digalactosyl diacylglycerols (DGDGs)	Inhibition of TPA-inducing formation	Breast cancer cells	NA	[37]
	D-K6L9	Reduce neovascularization	Breast and prostate cancer cell lines	PC-3, MCF-7	[51]
Brown seaweeds	Fucoxanthin	Apoptosis induction through up-regulating the expressions of beclin-1, LC3, and cleaved caspase-3 (CC3) and by down regulating Bcl-2	Gastric cancer	SGC7901	[52]
Spider/ Acanthoscurria gomesiana	Gomesin	Carpet model for destroying the membrane	Murine and human cancer cell lines along with melanoma and leukaemia	PC-3, MDA-MB-231	[53]
Cyanobacteria/ Hapalosiphon welwitschii	Hapalosin	Increasing the accumulation of drugs taxol and vinblastine in P-glycoprotein overexpressing cancer cell	Multi-drug-resistance (MDR), human ovarian cancer	SKVLB1 (adenocarcinoma cell line)	[54]
Marine sponges	Hemiasterlins	Inhibitory effect on microtubule assembly, cell cycle arrest, Apoptosis induction	Ovarian cancer cells	SKOV3	[55]
Fish / Mozambique Tilapia (Oreochromis mossambicus)	Hepcidin	Apoptosis induction	Human cervical carcinoma, hepatocellular carcinoma, breast adenocarcinoma cell line	HeLa, HepG2, MCF-7	[56-58]
Sponge/ Jaspis stellifera	Jaspamide (Jasplakinolide)KT2 and RT2	Caspase-3 activation and decreased protein expression of Bcl-2, induction of actin polymerization, Apoptosis induction	Prostate cancer cell, human promyelocytic leukaemia	HL-60, U937, THP-1	[59]
crocodile (C. siamensis)leukocyte	KT2 and RT2	These peptides act as death ligands and could upregulate death receptors including TRAIL R2, Fas and TNF RI.	NA	HeLa cells	[60]

Marine mollusk/ Elysia rufescens	Kahalalide F (KF)	Infraction of mitochondrial membrane and disrupts permeability of lysosomal membrane	Ovaries, breast, prostate, colon, and liver tumor cells	NSCLC, breast, hepatic, ovary, prostate and colon cancer cell line	[61]
Mangroveendophytic fungus / Lasiodiplodia sp. 318 #	Lasiodiplodin	Cytotoxic	Human cancer cell lines	THP1, MDa-MB-435, A549, HepG2, HCT-116 and THP1	[62]
Humans/ Homo sapiens	LL-37	Toroidal pore mechanism	Human oral squamous cell, carcinoma cells	PC-3, MCF-7, HT-29	[63]
Skin of African clawed frog, Xenopus laevis	Magainin	Induction of apoptosis	Human cervical carcinoma	HeLa cell	[64]
Fungi / Microsporum cf. Gypseum	Microsporins A and B	Inhibitors of histone deacetylase	Human colon adenocarcinoma	HCT-116	[65]
Housefly/ Musca domestica	MDPF	Inhibition via switching on the Th1-based protective cell-mediated immunity.	Sarcoma cancer	S180	[66]
Fungi /Microsporum sp., Aspergillus sp. and Eurotium rubrum	Neoechinulin A	Induce cell apoptosis via down-regulation of Bcl-2 expression, up-regulation of Bax expression and activation of the caspase-3 pathway	Human cervical cancer	Cervical carcinoma HeLa	[67]
Frogs/ Phyllomedussa bicolor	Phylloseptin-PH	Penetrating into the lipidic bilayer causing cell death	Breast cancer cells MCF7, breast epithelial cells MCF10A	HeLa, MCF-7, A549	[68]
Tunicate / Applidium albicans	Plitidepsin	Cell-cycle arrest, growth inhibition and apoptosis induction	Effective against various cancer types such as breast, thyroid, lung and so forth	Various cell lines such as PC12, HeLa cell, MDA-MB-231 and so forth	[69]
Fungi / Penicillium sclerotiorum M-22	Penicilazaphilones B and C	Cytotoxic	Human skin cancer and gastric cancer	B-16 (Melanoma cells), SGC-7901 (gastric cells) and M-10 (mammary epithelial cells)	[70]
Frogs/ Hoplobatrachustigerinus	Ranatuerin-2PLx	Cell apoptosis	Prostate cancer cell	PC-3	[71]
Fungi / Scopulariopsis brevicauli	Scopularide A and B	Growth inhibition	Pancreatic and colon tumour cells	Colo357, Panc89, HT29	[72]
Fungi / Simplicillium obclavatum EIODSF 020	Simplicilliumtides A, G, E, H	Cytotoxic	Human leukaemia	HL-60, K562	[73]
Horseshoe crab/ Tachypleus tridentatus	Tachyplesin	Disruption of plasma membrane by interacting with lipids	Prostate, Melanoma and endothelial cancer cell	TSU (prostate), B16 (melanoma)	[74]
Marine actinomycete/ Micromonospora marina	Thiocoraline	Arrest in G1 phase of the cell cycle, decrease the rate of S phase	LoVo and SW620 human colon cancer	NA	[75]

		progression towards G2/M phases			
Fungi / Calvatia caelata	Ubiquitin-like peptide	Ribonuclease and cell-free translation inhibiting activities	Breast cancer	Splenocytes cell lines	[76]
Fungi /Paecilomyces variotii EN-291	Varioloid A, B	Cytotoxicity	Human lung adenocarcinoma cells, colon carcinoma cells and hepatoma cells	A549, HCT116, and HepG2	[77]
Fungi / Aspergillus versicolor (ZLN-60)	Versicotides A and B	Cytotoxicity	NA	P388 cell line	[78]
Ascidian /Diplosoma virens Marine ascidians/Didemnum cuculiferum and Polysyncranton lithostrotum	Virenamides A–C	Inhibition of topoisomerase II enzyme	NA	P388, A549, HT29, and CV1	[79]
Ascidian / Diplosoma virens Marine ascidians/Didemnum cuculiferum and Polysyncranton lithostrotum	Vitilevuamide	Inhibition of tubulin polymerization	Lymphocytic leukaemia	P388	[80]
Fungi /Zygosporium masonii	Zygosporamide	Cytotoxicity	Central nervous cancer (CNS), renal cancer	NCI 60 SF-268 RXF 393	[81]

Table 1. Sources of Bioactive Peptides and Mechanism of Action on Different Cell Lines to Treat Different Cancer Types.

4. Production of Anticancer Peptides

Majority of research investigations have proven the beneficial biological effects of extracted peptides which are derived from plant or animal protein sources. The process of extracting a bioactive peptide from the original protein can be achieved in a number of ways including enzymatic breakdown, microbial fermentation and gastrointestinal tract digestion. Enzymatic hydrolysis is the main method used to produce bioactive peptides because it produces no toxic secondary metabolites and simulates gastrointestinal digestion which reduces reaction time. Commercially accessible enzymes such as pepsin, pancreatin, flavorzyme, alcalase, trypsin, chymotrypsin, and papain are used to extract bioactive peptides having anticancer potential [82].

5. Classification of Anticancer Peptides

ACPs can be classified into four typical classes, based on their secondary molecular structures [83]:

5.1. α-Helical anticancer peptides

One of the main groups of ACPs with short sequences made up of fundamental amino acids like arginine and lysine are the ones with α-helical structures. Two types of hydrophilic amino acids that helps to produce peptides with net positive charges at neutral pH are arginine and lysine which have amine and guanidinium groups in their side chains [84]. When compared to lysine, a stronger potential for electrostatic attraction and hydrogen bonding with a high affinity for the anionic membrane exists for arginine due to presence of guanidinium group [85]. On the other hand,

arginine is less hydrophobic than lysine with ε-amino groups in the side chain. The long, nonpolar alkyl side chain of lysine can be integrated into the hydrophobic region of the cell membrane which increases the cytotoxicity of α-helical ACPs against cancer cells [86]. ACPs' hydrophobicity can affect their biological activity in addition to their positive net charge [87]. ACPs often include up to 30% hydrophobic residues which causes the molecules to adopt a helical shape in hydrophobic environments with both polar and nonpolar faces [88]. Increased hydrophobicity on the nonpolar face of peptides increases their helicity and capacity for self-assembly allowing for a deeper insertion into the hydrophobic region of the cell membrane and consequently a greater chance of pore or channel formation in the membrane of the cancerous cell [89]. As a result, ACPs that are more hydrophobic have better anticancer and haemolytic properties against malignant cells. It includes bovine myeloid antimicrobial peptide (BMAP), melittin, cecropins and magainins.

5.2. β-Sheet anticancer peptides

The second class of ACPs exhibits a β-sheet structure with two to eight cysteine amino acids that forms one to four pairs of intramolecular S–S bonds with at least two β-strands. The creation of disulfide bonds in the β-sheet of ACP molecules is frequently necessary for the maintenance of the structural stability and biological functions of peptides. Amphipathic properties are also displayed by the β-sheet peptide which has polar and non-polar sections that are scattered spatially. After connecting with phospholipid membranes, ACPs do not undergo conformational changes due to their highly stable β-sheet architectures. One of the more studied cationic ACPs is defensin which has residues ranging from 29 to 45 amino acids. An ACP called defensin is made up of three to six disulfide bonds that produce hydrophobic and hydrophilic domains that are spatially separated in cyclic triple-stranded β-sheet structures. Moreover, the types of defensin can be identified by the position and configuration of intramolecular disulfide bonds in the peptides. For example, α-defensin has disulfide bonds in positions Cys1–Cys6, Cys2-Cys4 and Cys3–Cys5, while β-defensins are characterised by Cys1–Cys5, Cys2-Cys4 and Cys3–Cys6. Defensins capacity to fight cancer is largely dependent on their ability to form cyclic cysteine ladder conformation which maintains the cyclic backbone's structure and molecular stability. The capacity and selectivity to bind with cancer cells are enhanced by the stable cyclic structures, large surface area and decreased conformational flexibilities [90].

5.3. ACP's with elongated formations

Amino acids including arginine, proline, tryptophan, glycine and histidine are commonly enriched with elongated ACP forms but they lack in traditional secondary topologies. Only non-covalent interactions such as hydrogen bonds can stabilise the stretched structures [91]. PR-39 is typically a linear ACP that is isolated from swine neutrophils and composed of proline (49%) and arginine (24%) having 39 amino acid residues and it is an irregularly shaped protein [92]. Through the induction of syndecan-1 expression, PR-39 demonstrates anticancer activity on human hepatocellular carcinoma cell lines. Another class of ACP produced from glycine-rich insects is Alloferon which can activate natural killer cells. [93]

5.4. Cyclic anticancer peptides

The head-to-tail cyclization peptide backbone or disulfide connections that make up cyclic ACPs exhibit far greater stability than linear molecules [94]. Diffusa cytides 1-3 are novel cyclic peptides that were isolated from the white snake plant's leaves and roots. They have been shown to inhibit the development and migration of prostate cancer cells in vitro [95]. Another cyclic pentapeptide, H-10 has shown to be cytotoxic to mouse malignant melanoma B16 cells in a concentration-dependent manner but it does not appear to be cytotoxic to human peripheral lymphocytes or rat aortic smooth muscle cells [96, 97]. Cyclic ACPs make up the majority of ACPs in therapeutic trials

due to their potent inhibitory effect against cancer cells.

In conclusion, since time immemorial, natural products have played a significant role in drug development and pharmacotherapy particularly in the treatment of cancer. Currently there is a heightened focus on identification of anticancer drugs that are highly effective with minimal toxicity. It is thought that biologically active peptides derived from natural sources have a variety of functions such as antibacterial, anticancer and antioxidant potential. There is growing evidence that naturally occurring biopeptides with carcinogenic properties can cause cell death by binding to several different cellular proteins and initiating the apoptotic process through both extracellular and intracellular pathways. The review aims to summarize the various natural peptides obtained from various sources and highlights the property, classification and mechanism of action on various cell lines. Therefore, peptides being safer, highly selective, efficacious and well tolerated has garnered interest of patients as a better alternative for cancer therapy and it will help broaden the applicability of bioactive peptides as potent therapeutic agents for the treatment of unmet medical needs of cancer.

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Statement of Transparency and Principals:

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee

of author affiliated Institute.

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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