IJPSR (2025), Volume 16, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 March 2025; received in revised form, 28 April 2025; accepted, 30 June 2025; published 01 September 2025

RECENT ADVANCEMENT IN THE DEVELOPMENT OF THERAPEUTIC PEPTIDES

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Keywords:

Peptides, Cyclization, Oxytocin, Vasppressin, Neurotransmitters

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ABSTRACT: Peptides are naturally occurring biologics, which provide essential functions as hormones, growth factors, biological messengers, anti-infective, neurotransmitters, and antimicrobials. Peptide hormones such as insulin, vasopressin, oxytocin, and gonadotropin-releasing hormone have significantly accelerated advances in modern drug development fields, including biology, chemistry, pharmacology, and other cutting-edge technologies. This review article described the peptides, their different sources and production processes, and how they are synthesized. Peptides are highly desirable as therapeutic agents due to their unique properties, which are determined by their physicochemical and proteolytic stability profiles. Numerous techniques are being developed to enhance the therapeutic profile of peptides, such as side chain modification, cyclization, N-methylation, peptoids, and substitution with D-amino acids inclusion in delivery systems and halogenation. Peptides are therapeutically used in the management of several diseases; the potential range of peptide-based medications is being extended to new targets by ongoing research.

INTRODUCTION: Food is thought to contain physiologically active substances in addition to dietary ingredients that may improve human health and overall body condition. Naturally occurring biologics, peptides range in length from 2 to 50 amino acids and provide essential functions as hormones, growth factors, biological messengers, anti-infectives, neurotransmitters, and anti-microbials. Peptide hormones, such as insulin, vasopressin, oxytocin, and gonadotropin-releasing hormone, have significantly accelerated advances in modern drug development fields, including biology, chemistry, pharmacology, and other cutting-edge technologies [1-3]. A major scientific achievement in 1921 was the identification of insulin, which later became the first peptide medication to be produced for profit.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(9).2454-67

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(9).2454-67

This finding made it possible to identify and evaluate additional therapeutic peptides and produce treatments based on peptides. Due to peptides being comparatively safer because of their short half-life, low toxicity, and great specificity, selectivity, and effectiveness. Insulin has benefited numerous diabetic patients since it was first introduced to the market in 1923. Still, in the 20th century, Given the high market demand and the fact that animal-derived insulin, such as that which was used to control the insulin market for nearly 90 years until synthetic insulin replaced it, human insulin manufacturing was unable to keep up [4-5].

The synthesis and usage of short chains of amino acids for a variety of uses in medicine, cosmetics, and research is the main emphasis of the peptides market. This market is developing significantly due to increased interest in peptide-based therapies and medication development. Market dynamics are nevertheless impacted by issues like exorbitant production prices, complicated regulations, and little stability [7]. The conditions for the prompt launch of peptide-based drugs onto the global market have been made possible by advancements

in sequencing technology with high throughput and the growth of computational and experimental methods for collecting data. At the moment, for individuals with a variety of illnesses, there are more than 100 licensed peptide medications available on the market, and numerous Preclinical and late clinical trials are being conducted for further peptide-based medicines [8].

Comparatively speaking, the manufacturing of biologic drugs based on peptides is less expensive and difficult than the conventional drug development method [9]. Consequently, the recognition of peptides having restorative properties is crucial for creating novel, efficient therapeutic medications, which quickens their application in medical care [10]. As such, there is enormous promise for finding new, generic, and expandable experimental solutions for accurate prediction of medicinal peptides.

Types of Peptides:

Class A: In this group the modified peptides that resemble natural peptide binding epitomes since they are primarily made of proteogenic amino acid. The aims of introduced alterations are often to improve the peptides oral availability, cell permeability, stability or affinity for a chosen binding partner. Designing class A peptidomimetics usually involves the use of macrocyclization techniques, such as stapled peptides [11-12].

Class B: This category of peptidomimetics have peptides that include a large amount of non-natural amino acids, significant backbone alterations, or bigger non-natural building pieces that mimic the structure of a the arrangement of a certain peptide binding motif. Example D-peptide and peptide foldamers such beta –peptide.

Class C: If we compare structural mimetics to their parent peptide sequence, several compounds have undergone major changes. A small molecular scaffold is typically attached to project groups in a manner similar to peptides bioactive.

Class D: By mimicking a peptides mode of action, these mechanistic mimetics avoid directly replicating its side chains or structure. Taken by compound library testing, class D peptidomimetics can be developed using a short peptide sequence. Example Nirmatrelvir is an orally- active the have small molecule drug derived from Lufotrelvit [12-14].

Production of Bioactive Peptides: There is a various methods have been developed for BP. Reliability, biocompatibility, industrialization potential, and low cost are the best methods. They create certain peptides with unusual amino acids or unique functional groups, such as sugars or fatty acids, for which post-purification engineering and/or output are required. Food supplements are less common than medications [15].

Enzymatic Hydrolysis: There are three ways for performing the enzymatic hydrolysis of bioactive peptides from precursor proteins.

1. Enzymatic hydrolysis that are derived from plants and microorganisms.
2. Using digestive enzymes.
3. Microbial fermentation [16].

The most popular method for producing bioactive peptides is the employment of specialized or even nonspecific proteases, since this method allows for better control over the hydrolysis process and produces peptides with desired molecular weights more quickly. And the makeup of amino acids. Several enzymes, including pepsin, bromelain, and Papain, trypsin, and chymotrypsin are utilized at the ideal pH and temperature. Circumstances. Digestive enzymes are primarily used in the production of several recognized bioactive peptides such as trypsin and pepsin. For example Trypsin is commonly utilized to make calcium-binding phosphopeptides and inhibitory peptides for the enzyme that converts angiotensin (ACE) [17-18].

Enzymes with coatings permit more regulated and moderate enzymatic hydrolysis. Furthermore, it is possible to recover these frozen enzymes in order to stop enzyme autolysis from producing secondary metabolites [19]. The type of enzyme utilized, the kind of protein precursor, the extent of hydrolysis, and the technique used to separate the final sample all affect the final product of enzymatic hydrolysis. While there are differences in the uses of crude and refined peptides, it is preferable to employ cruder forms of peptides in order to lower the final cost [20].

Chemical Synthesis:
There are two types of Methods:

1. Solid Phase Synthesis:
2. Solution Phase Synthesis:

Solid Phase Synthesis: Merrifield initially presented solid phase synthesis in 1963. To create a linear peptide chain, amino acids are added one after the other. The first amino acids C-terminus is covalently bonded to resin, a solid support, and the amino acid chain binds starting at the N-terminal. For every amino acid added to the peptide chain, the following four chemical reactions are repeated: de-protection, activation, coupling, and resin breakdown [21].

1. To allow access to alpha-amino group at end of the peptide chain, protected amino acid is removed.
2. The next amino acid to be supplied is transferred into an active ester through activation.
3. The next amino acid that continues to be supplied is transformed into an active ester through activation. The active ester and the de-protected alpha-amino group at the end of the peptide chain combine to form an amide bond during coupling. Following coupling, the subsequent de-protection triggers a fresh cycle of synthesis.
4. Depending on the type of resin utilized for solid support, different chemicals are used for resin cleavage. During cleavage, the side chain protective groups are also removed [21].

Solution Phase Synthesis: Scientists initially developed the standard technique known as solution phase synthesis for the production of peptides. This technique couples an N-terminally protected amino acid with the C-terminal of one amino acid that is protected by an ethyl methyl ester. Proceed to the next coupling after isolating and purifying each coupling peptide [22].

Where Bioactive Peptides Come From: Any organism can produce or isolate peptides with potential bioactivity. However, there are a few things to think about while choosing a host. On the one hand, it should be noted that the method of extracting and purifying the peptide in question will ultimately depend on the choice of target host. However, it should be remembered that the host's production of the target peptide must be extremely high. In order for its manufacturing and purification to be both financially feasible and problematically valuable to go on [23].

- Animal sources
- Plant sources

Animal Sources: Animal protein-derived peptides have been research investigated for a variety of health benefits [24]. About 20% of proteins can be found in blood, making it a valuable and possibly beneficial source of BP. While meat processors face a serious issue with blood disposal, A little study has-been done on serum albumin, the primary blood protein. A recent study used different amounts of trypsin to hydrolyze serum albumin, and the peptide sequences in the hydrolysates displayed extra tasks: converting enzyme for angiotensin (ACE) inhibition (activity against hypertension), DPP-IV inhibition (control of glucose), and antioxidant [25]. Peptides found in marine species have been shown to induce cell death by a variety of pathways, such as apoptosis, modulation of the tubulin–microtubule balance, prevention of angiogenesis, ant proliferative actions, and cytotoxic effects. These details have presented using marine bioactive peptides as a novel approach to produce novel chemicals for biological investigation [26].

Milk Product: The best sources of animal bioactive peptides are dairy products like milk and cheese. Given that milk plays an important part in providing young mammals with nitrogen and protein from a young age, it is evident that milk is a valuable food source when it comes to protein content. The milk's proteins have significant characteristics including antimicrobial, ant oxidative, and immune-boosting effects. The quantity of these qualities is growing daily, and lately, particular focus has been placed on the function of casein proteins as chaperones in milk. Oxygen peptides in milk, as they relate to There have been reports that milk has effects on the central nervous system similar to those of morphine [27].

Egg Product: Egg white protein powder (EWPP) is employed today in various food and pharmaceutical industries because of its rich source of amino acids and long shelf life [91]. There have been major efforts to remove eggs through the process of enzymatic digestion. Thus, enzymes like thermolysin, pepsin, and Trypsin, alcalase, and chymotrypsin have all been utilized [28-29].

Meat Product: A few additional species may also be a major source of BPs in addition to the ones mentioned here. For example, a number of Gram-negative and positive bacteria secrete peptides known as bacteriocins, which are antimicrobial peptides containing neutral or positively charged peptides. These peptides do not contribute to the defense against viruses Infection but aid in the bacterial killing of rivals in the struggle for environmental nutrients [30-31].

Plants Sources: Peptides derived from plants have historically received less attention than those derived from mammals. However, it should be mentioned that plant proteins are major sources of unsaturated fatty acid-free proteins that can include beneficial components. Lately, specific actions have been found in peptides generated from plants that have significant roles in people. Opioid, immunostimulatory, antibacterial, hypo-cholesterolemic, and ant diabetic among these advantages include antioxidant and antihypertensive properties [32].

Artificial Intelligence to Find New Peptide Drugs: Numerous sophisticated techniques for creating therapeutic peptides using computer techniques have already been documented [33, 34]. A peptide sequence created from scratch (de novo) or a peptide scaffold with the appropriate bioactivity (a seed peptide) isutilized as a springboard. The peptide sequences are iterated and optimized using *in-silico* techniques like machine learning and deep learning. Bioactive peptides have been identified using these techniques. For instance, to create antimicrobial peptides with 80%prediction accuracy, Haney and colleagues developed a quantitative structure-activity relationship (QSAR) model [35]. Capecchi *et al.* recently used machine learningmodels to find antimicrobial peptides that damage membranes. The model not only found peptides with enhanced antimicrobial activity but also found peptides with low toxicity to human erythrocytes, which solved a major problem for earlier attempts to find antimicrobial peptides [36].

Techniques to Improve Peptide Stability and Bioactivity: Lead peptides might be promising therapeutic agents, but they might not be strong enough or stable enough to be considered viable medication candidates. Researchers have investigated a number of chemical modification methods to improve the stability and bioactivity of peptides, comprising side chain halogenations, N-methylation, peptoids, cyclization, D-amino acid substitution, and terminus protection [37, 38]. Cyclization has been the most effective and popular method for maximizing the bioactivity of peptides, despite the fact that some of the alterations have been successful in creating peptide medications. This is because it has been demonstrated that cyclization provides peptide medications with a number of benefits. Thus, it should come as no surprise that two-thirds of all authorized therapeutic peptides are cyclic peptides [39].

Cyclization: A popular and somewhat easy chemical technique for giving linear peptides and peptidomimetics a number of advantageous properties, including improved stability, high cell permeability, and better target specificity and selectivity, is cyclization [40]. Due to cyclic peptides have a set geometry that lowers the entropic cost of binding, enabling more effective and targeted binding On the other hand, the considerable structural flexibility of linear peptides may lead to off-target and promiscuous interactions as well as a higher risk of unfavorable side effects [41]. There are various forms of cyclization, including side chain to side chain, end-to-side chain, and end-to-end (head-to-tail) cyclization (produced between either of the terminals and an amino acid side chain).Stapled and bicyclic peptides are examples of additional cyclization variations.

Cyclic peptides can be employed as therapeutic agents in imaging, diagnostics, RNA binding, enzyme inhibition, and the modification of protein-protein interactions. Consequently, it is anticipated that the application of macrocyclic peptides would increase rapidly [42]. Even at a modest dosage of 0.5 mg/kg, cyclization produced a peptide derivative with greater therapeutic efficacy, increased

bioactivity, and improved proteolytic stability [43]. This study showed that the development of peptide medications can benefit greatly from the use of macrocyclization scanning particularly when the peptide-receptor complex's structural characterisation is lacking.

D-amino Acid: The body's natural proteins and peptides are made up of L-amino acids, which can be broken down by enzymes. These enzymes normally recognize the structures of L-amino acids, while D-amino acids are more resistant to them. Consequently, replacing the proteolytic stability of therapeutic peptides can be increased by combining L and D amino acids [44]. Additionally, D-amino acid substitution can lessen the toxicity of peptide-PEG conjugates in animals as well as the production of anti-PEG antibodies [45]. D-amino acids can generally be used to completely or partially substitute peptides. It is crucial to remember that while replacing L-amine acids with D-amino acids improves a peptide's proteolytic stability; it may also affect the peptide's bioactivity.

This is due to the shape of the peptide and how it interacts with its target can be changed by adding D-amino acids. As a result, it is imperative to make sure that adding a D-amino acid doesn't drastically change the secondary structure of the peptide. Restricting D-amino acid replacement to the peptide termini is one strategy.

The D-amino acid scan is a widely used method for investigating how the stereochemistry of amino acids affects the structure and functionality of peptides. For instance, the essential stereocenters of α-Conotoxin were identified using a D-amino acid scan. Nicotinic acetylcholine receptor antagonists include RgIA. Analogue 13 maintained full activity and demonstrated enhanced stability against enzymatic degradation in human serum and simulated intestinal fluid (SIF), whereas the majority of analogues shown a decrease in biological activity [46]. Likewise, the antimicrobial peptide W3R6 was shown to have a partly substituted analog, D-Arg-W3R6. The fully substituted D-enantiomer, D-W3R6, had reduced antibacterial activity, whereas it displayed the same antimicrobial activity as the original peptide. D-Arg-W3R6 and D-W3R6 both demonstrated enhanced proteolytic stability [47].

One possible cancer immunotherapy drug is the D-peptide that was discovered to disrupt the immunological checkpoint TIGIT [48]. This technology's primary drawback is that it produces target proteins in D-form. Calculation this is yet another novel approach to D-form peptide de novo design. Yang *et al.*, for instance, created D-peptides from scratch that attach to tumor necrosis factor-α (TNFα) and prevent it from interacting with its receptor 1 (TNRFR1) [49].

Peptoids: Because they lack amide linkages in their backbone, peptidoids peptidomimetics contain N-substituted glycines, which enhance proteolytic stability. Peptoids can be easily created utilizing solid-phase synthesis methods and share a structural pattern with peptides [50]. By replacing amino acids, peptidoids can be foundcontains traces of peptoid. For instance, Kessler *et al.* produced a series of highly stable triple-helical collagen mimic peptoids by adding N-substituted glycines to collagen-mimetic peptides (CMPs). These peptoids have the potential to be employed as materials and therapies that mimic collagen [51]. A combinatorial library of peptoids is screened against a particular target as an additional method of finding peptoids.

Spicer et al. used the peptoid library agar diffusion (PLAD) assay tofound a tripeptoid named AEC5, which showed promising antifungal activity against C. neoformans and destroyed all viable fungal cells in a matter of hours [52]. In a different study, cyclic peptoid inhibitors of cyclophilin D were found to be potential neuroprotective agents using a one-bead-one-compound (OBOC) library of cyclic peptoid. The most effective anti-inflammatory peptoid with minimal cytotoxicity was found to be peptoid I11, which showed a high permeability across the blood-brain barrier (BBB), suggesting that it could modulate mitochondrial function in neuronal cells. Peptoids are more promising than peptides in combinatorial library screening because of their high proteolytic stability [53].

N- Methylation: An essential chemical change for enhancing the drug-ability and pharmacokinetic characteristics (i.e., absorption, half-life, and bioavailability) of therapeutic peptides is alkylation of the nitrogen atom in peptide amide bonds of the different N-alkylation.

N-methylation is the most popular technique because to its adaptability and simplicity of synthesis. It makes it easier for peptides to adopt a cis confirmation and increases steric hindrance [54]. For example, McBrayer and associates showed that peptides with N-methylation have a notable increase in proteolytic stability. The half-life of E. faecalis fsr quorum sensing regulating peptides was more than six times longer when N-methylation was present [55]. The functional selectivity of human urotensin II and similar peptides to their targets has been investigated using the idea of successive backbone N-methylation. The findings showed that the biological activity of the peptide can be influenced by the placement of the N-C link emphasizing how important hydrogen-bond interactions are to these endogenous peptides' bioactivity [56].

N-methylated peptide inhibitors of neutral endopeptidase (NEP), aminopeptidase N (APN), and angiotensin converting enzyme (ACE) were assessed in a different investigation using their native substrates. Peptide compounds with improved action against hypertensive, hypertrophic, and fibrotic conditions were produced by N-methylation [57]. The inefficiency of coupling during peptide synthesis and the challenge of chemically synthesizing N-methyl building blocks are the obstacles of the backbone N-methylation technique. Lately, A chemoenzymatic approach has been devised by researchers to get around this restriction. By conjugating peptides to the catalytic scaffold of a borosin-type methyltransferase, they were able to achieve N-methylation. Effective Nmethylation was demonstrated by the peptides conjugated to the transferase, and the resulting N-methylated peptide is cleavable from the scaffold [58].

Side Chain Halogenations: A new technique for adjusting the pharmacological properties of organic compounds, such as peptides, is halogenation. Iodine, bromine, chlorine, and fluorine are halogens that have been added to different medicinal compounds to enhance theirbioactivity. Particularly, efforts to find new drugs have made considerable use of fluorine and chlorine. Improved cell membrane permeability, increased target selectivity, and less adverse effects are typically linked to halogenation [59]. For instance, RGD peptides' affinity and specificity for integrin αvβ3 were enhanced when halotryptophans were added [60]. Likewise, the impact of changing out different halogens on peptoids' antimicrobial properties was investigated. It was shown that adding bromine or chlorine increased the antibacterial effectiveness against Gram-positive bacteria, while Fluorination had no discernible impact. Although halogenation can give peptide medications advantageous characteristics, halogenating polar groups may make the peptide more hydrophobic, which can lead to aggregation and decreased effectiveness [61].

In the search for clinically beneficial peptides, other chemical changes of therapeutic peptides have also been investigated, albeit less frequently. These include lipidation, PEGylation, termini protection, decreased peptide bonds, the use of amide bond surrogates, and various polymer-peptide conjugations. Other references have provided further detail on these changes [62–64].

Mechanism of Action Peptides: Because of their benefits, which include high selectivity, high affinity for targets, and low side effects, peptides have seen an increase in therapeutic applications in recent years [65]. Different strategies are used by peptide medicines to affect cells. A few some peptides attach to cell-surface receptors, whereas others enter cells and work in the cytoplasm. However, only a small percentage of peptides may enter cells because of their weak membrane permeability [66, 67].

Cell-penetrating or cyclic peptides are more effective at penetrating membranes. These peptides can pass through the membrane by endocytosis, passive diffusion, or the creation of membrane holes. Hydrophobic peptides have a higher propensity to pass through cell membranes directly [68]. Furthermore, clathrin-mediated or clathrin-independent endocytosis can allow positively charged peptides to enter the intracellular space of cells [69]. Additionally, peptides can work byattaching to receptors on the cell surface. The ligand-receptor signaling is changed when peptides attach to receptors. While antagonistic peptides have the ability to impede or decrease downstream biological functions, agonistic peptides have the ability to promote them [70].

Anti-viral AMPs: AMPs with virus-targeting capabilities often contain mechanisms that target both DNA and RNA viruses; however they can be categorized into three types based on how they behave. AMPs that target the viral envelope make up the first one. AMP LL-37 is one example of how they work by embedding themselves in the virus's envelope, which causes instability and interferes with the virus's mechanism of action. By attaching themselves to target cells, AMPs can inhibit viruses' ability to bind to particular receptors on those cells, which is their second mechanism of action [71, 72, 73]. Defensins, for instance, can attach to the glycopeptides of the herpes simplex virus and stop it from attaching to the receptors on the target cell . The third class of AMPs that fight viruses includes those that interfere with viral transcription, target the viral nucleocapsid, damage or inhibit specific viral proteins, or stop the virus from exiting the host cell in order to target internal components [71, 72, 73, 74].

Antibacterial AMPs: Antibacterial AMPs interact with negatively charged bacterial membranes to cause instability and disruption; they are primarily cationic and amphipathic. Gram-negative bacteria are their main target, however some AMPs, have a wide range of activity against Gram-positive bacteria, including daptomycin. By attaching themselves to cell wall precursors, glycopeptides prevent the synthesis of peptidoglycan. Additionally, AMPs have been proposed as an H. pylori therapy approach [73]. Although AMPs can employ both processes, antibacterial AMPs primarily target either the bacterial membrane or the non-membrane [75, 76, 77, 78].

Membrane-Targeting AMPs: To create pores and channels in the cell wall, a positively charged and amphipathic AMP binds to a negatively charged and hydrophobic phospholipid in the cell membrane, as was previously mentioned. This is the cell-membrane-targeting mechanism used by a variety of antibacterial AMPs [79, 80, 81, 82]. Consequently, there are currently five cell membrane models. The barrel-stave, toroidal-pore, carpet, aggregate channel, and flood gate mechanism models are among the ways of action that have been explained. Cytoplasmic outflow, membrane collapse, permeability, and ultimately cell death are caused by the pores created in the barrel-stave model [83]. Alamethicin, protegrins, and ceratotoxins are AMPs that employ this method of action, among others.

The toroidal-pore concept states that AMPs can interact with the lipid head groups to pass through the lipid membrane. This bends the lipid bilayer, allowing the peptides to enter the membrane bilayer and create channels and pores. AMPs that employ this method of action include melittin, actinoporins, protegrins, and magainins [79, 80, 81].

AMPs blanket the cell membrane in the following manner, which is referred to as the carpet model. Surface like a carpet and engage with the phospholipid head groups of the membrane. This leads to high peptide concentrations and ultimately the degradation and penetration of the phospholipid bilayer. AMPs such as cecropins, magainin, and indolicidin use this mode of action. According to the aggregation channel paradigm, AMPs spontaneously create unstructured peptide aggregates that encircle the membrane of the pathogen. Cytoplasmic fluid leakage and channel development result from this the final model is the floodgate mechanism, a newly proposed mechanism. α-helical AMPs create temporary toroidal holes in the pathogen's cell membrane early in the attack. According to one theory, AMPs initially strain the hydrophobic and electrostatic membrane before enlisting the help of neighboring unbound peptides [82, 83, 84].

Non-Membrane Targeting: Through endocytosis, several AMPs can enter cells directly. They can target RNA, DNA, or protein synthesis in this manner, or they can directly affect intracellular proteins and significant bacterial organelles. AMPs focus on the production of proteins and nucleic acids by attaching itself to them and breaking their structure. Histone-derived AMPs like buforin II and indolicidin, which are effective against both Gram-positive and -negative bacteria, are the ones that exploit this mechanism the most. Targeting the enzymes and proteins involved in specific metabolic pathways is an additional method of identifying and preventing the creation of nucleic acids and proteins [85, 86]. For instance, indolicidin can block double-stranded DNA relaxing by acting on type I DNA topoisomerase. RNA polymerase, DNA gyrase, and other DNA can be affected by

more AMPs. Proteins linked to replication. The nucleic acid damage repair pathways are another target of AMPs; they can interfere with signaling and damage response pathways to encourage apoptosis and cell death. By affecting the translation pathway, which is often brought on by proline-rich AMPs, some peptides can also target ribosomes to prevent the creation of proteins. Additionally, PrAMPs can influence protein folding and assembly by blocking the bacterial heat shock protein [85, 86]. There are two main categories of peptides depicted: membrane-bound and outer layer, denoted by "1," which is the pathogen cell's cytoplasmic membrane, and AMPs, denoted by "2." Peptides that are membrane-bound aresymbolized by five mechanisms: the aggregate channel, floodgate, carpet, toroidal, and barrel-stave models. The intracellular AMPs, denoted by the numbers "3" through "7," exhibit the inhibition of enzymes necessary for the binding of structural proteins of the cell wall, the synthesis of DNA and RNA, ribosomal functions and chaperone proteins, and cellular respiration through the production of ROS (Reactive Oxigen Species), ATP (Adenosine Triphosphate), and NADH can be seen in diagram. **Fig. 1** [84] (Created in biorender.com).

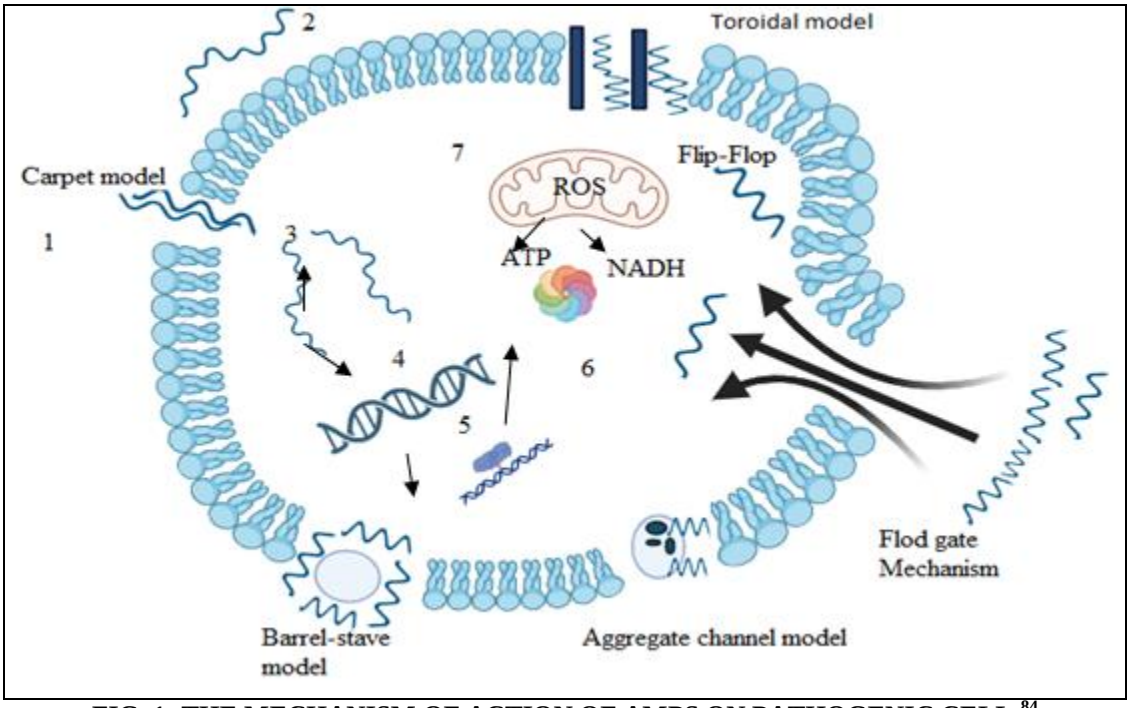

FIG. 1: THE MECHANISM OF ACTION OF AMPS ON PATHOGENIC CELL [84]

TABLE 1: PEPTIDE DRUGS APPROVED BY US- FDA (2019-2023)

S. no.	Dugs	Approved	Indication	Mechanism
1	Bremelanotide	US-FDA 2019	Treatment of Hypoactive sexual desire disorder(HSDD)	A melanocortin receptor agonist that activates pathway in the brain associated with sexual desie.
2	Lusutrombopag (Mulpete)	FDA,2018	Thrombocytopenia in adults with chronic liver disease undergoing medical procedure	A small-molecule thromboprotein receptor agonist.
3	Eptinezumab (Vyept)	FDA,2019	Prevention treatment of migraines	Calcitonin gene related peptide(CGRP) Antagonist
4	Afamelanotide (Scenesse)	FDA, 2019	Pain and injury to the skin	13 aa lineal peptides that are comparable to α-MSH
5	Enfortumab Vedotin-Ejfv (PADCEV)	FDA, 2019	Cancer expressing Nectin-4	ADC binding to cells that express nectin-4, The ADC-Nectin-4 complex is then internalized, and MMae are released through proteolytic cleavage [87]
6	Setmelanotide (Imcivree)	FDA, 2020	Chronic Weight management	Melanocortin-4 receptor (MC4) Activator

7	1164Cu-DOTATATE	FDA, 2020	Scintigraphic imaging	Somatostatin receptor agonist
8	Piflufolastant F18 (Pylarify)	FDA, 2021	Prostate-specific Positron Emission Tomography (PET) Men with prostate cancer who have positive lesions for the membrane antigen (PSMA)	PSMA targeting
9	Difelikefalin (Korsuva)	FDA, 2021	Pruritus associated with chronic kidney disease	Kppa opioid receptor agonist
10	9 Odevixibat (Bylvay)	FDA,2021	Pruritus in patient aged over 3 months with progressive familia intrahepatic choleestasis	Inhibitor of ileal bile acid transporter [87]
11	Vosoritide (Voxzogo)	FDA, 2021	Achondroplasia	C-Type natriuretic peptide analog
12	Voclosporin (Lupkynis)	FDA, 2021	Lupus nephritis	Calcineurin inhibitor
13	Tirzepatide (Mounjaro)	FDA, 2022	Type 2 diabetes	Glucagon- like peptide -1 agonist
14	Lutetium Lu-177 vipivotide tetraxetan (Pluvicto)	FDA, 2022	PSMA, or prostate-specific membrane antigen, Castration-resistant prostate cancer with positive metastases	PSMA Targeting
15	Terlipressin	FDA2022	To enhance renal function in persons suffering from hepatoenal syndrome with a sharp decline in renal function	V1 and V2 receptors [87]
16	Zavegepant (zavzpret)	FDA,2023	Acute treatment of migrane with or without aura in adults	Calcitonin gene – related peptide receptor antagonist
17	Rezafungin (Rezzayo)	FDA,2023	Candidemia and invasive candidiasis in adults	Serves as a concentration-dependent *in-vitro* fungicidal agent and breaks down the cell wall of fungal species, including Candida spp. [88]
18	Motixafartide (Aphexda)	US- FDA	Use in conjunction with filgrastim to stimulate the production of hematopoietic stem cellsto the peripheral blood in patients with multiple myeloma for collaction and subsequent autologous transplantation	C-X-C Chemokine receptor type 4 inhibitor [88]
19	Trofinetide (Daybue)	US-FDA	Rofinetide is recommended for the management of adult Rett syndrome andpediatric patients that are at least two years old	Linked to loss-of-function mutations in the gene that codes for the DNA binding protein methyl CpG binding protein 2 (MECP2), which plays a part in the epigenetic control of gene expression.
20	Zilucoplan (Zilbrys)	US- FDA	Zilucoplan is recommended as either the primary or supplemental treatment for conventional treatment for adults with generalized myasthenia gravis (gMG)	Attaches itself to a specific terminal complement protein spot. C5 and stops C5 from cleaving into C5a and C5b, which stops the MAC from assembling C5bdependently [88]

Challenges and Future Perspective: The generation, separation, and purification of peptides are the main issues in this subject. Their business or Production in a lab is costly and time-consuming. Additionally, assessing a peptide's effectiveness, its mechanism of action in the body and pharmacokinetic analyses is also difficult. To fully comprehend their impact on the absorption, distribution, metabolism, and excretion of peptides, numerous studies have been carried out. It is challenging and costly to obtain precise information regarding the pharmacokinetics of these peptides *in-vivo*. Many scientists exclusively investigate the efficacy of peptides *in-vitro* because of these problems. Furthermore, there aren't many researches investigating the potential of pure

peptides against particular indicators. Therefore, more study should be done to address these issues. Excellent and reasonably priced technologies for peptide fraction separation and enrichment should be introduced in order to boost the yield of BAPs. *In-silico* methods (molecular docking) and in-vivo research should be performed to assess the pharmacokinetic characteristics of BAPs in order to verify their effectiveness. To increase their bioavailability, substances including chelators, fatty acids, acyl-carnitines, bile salts, surfactants, and anionic/cationic polymers can be used. Nanotechnology and controlled delivery systems should be employed to shield the BAPs from the body's hostile environment. Additionally, more research on synthesized pure peptides is required, and *in-vivo* animal and clinical investigations are required to corroborate the results of *in-vitro* studies [89].

Peptides have developed a distinct therapeutic niche from their modest origins as compounds extracted from cattle glands and will remain a crucial component of the pharmaceutical industry scenery. Therapeutic peptides have kept up with scientific innovation by utilizing modern chemistry techniques to broaden molecular targets and indicators, as well as by variety, as well as by the invention of improved medicinal qualities. We think that more peptide prospects will be found through study. The list of peptide medications frequently used in medicine serves as an example of how peptides are a natural starting point for drug development since they are endogenous ligands for peptide hormone receptors practice. Over the past five years, authorities have authorized Guanylyl cyclase C (GC-C)-targeting first-in-class peptides and two near analogs of native peptides that bind to the melanocortin 1 receptor (MC1R): linaclotide and afamelanotide, respectively. These approvals provide as an example of the ongoing potential for innovative peptide treatments [90].

The potential range of peptide-based medications is being extended to new targets by ongoing research. Numerous peptide-addressable targets that do not currently have licensed medications have demonstrated therapeutic promise in preclinical illness models or early-stage clinical studies. For instance, kisspeptin analogs that target GPR54 may be advantageous to currently utilized medicines for aided reproduction, [91] and an agonist of the melanocortin 4 receptor (MC4R) might Patients with hereditary obesity syndromes should lose weight [92]. Drug companies have submitted patent applications for apelin derivatives, which are endogenous peptides [93, 94]. neuromedin U [95, 96] and adrenomedullin, [97] according to findings from research on animals. To the best of our knowledge, peptides from the last two drug development programs have not been tested on humans, and a putative derivative of apelin has just lately entered clinical trials [98].

Peptide drug discovery will continue to be aided by advancements in computational biology and peptide screening. Using proteomic, genomic, and metabolomic screening of toxins and other natural product sources, bioactive peptides with distinctive structural characteristics produced by rare post-translational modifications or non-ribosomal production can be found [99, 100]. An enhanced knowledge of the molecular causes of genetic diseases in humans can produce fresh, promising therapeutic leads, [101] and the de-orphanization of peptide receptors with inadequate characterization can encourage the search for novel receptor-ligand combinations [102].

Finally, new approaches to peptide medication formulation, transport, and half-life extension will make this unique family of molecules more accessible. There are initiatives to increase the oral availability of peptide treatments by improving the stability of the medication in the GI tract in creating peptides with enhancers of permeability, [103, 104] and increasing the peptides' availability in the central nervous system by conjugating them to carrier molecules or delivering them in nanoparticle form [105, 106].

CONCLUSION: In recent decades, peptides have drawn a lot of attention, and the number of peptide-based biotherapeutics that have been approved has been rising annually. Over 80 peptide drugs are already available, and severalnovel medicinal peptides are in preclinical trials and research studies, and this advancement will greatly simplify in the upcoming years. The difficulties in delivering many medications based on peptides are being effectively resolved with the evolution of the many tactics covered in this review. Peptide

medications have been used to treat a variety of illnesses, including diabetes, cancer, heart disease, gastrointestinal disorders, infectious infections, and vaccination progress. Given their enormous medicinal potential, the market opportunities, and financial benefits, we anticipate that therapeutic peptides will keep funding and research initiatives coming in order to sustain success.

ACKNOWLEDGEMENTS: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Kumar S and Srivastava V: Recent advancement in the development of therapeutic peptides. Int J Pharm Sci & Res 2025; 16(9): 2454-67. doi: 10.13040/IJPSR.0975-8232.16(9).2454-67.