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Peptide-Based Drugs: Development and Therapeutic Applications

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ABSTRACT

Current advances in knowledge about peptides as drugs are of great significance; They have planning potentialities in different sections of medicinal practice. This review will summarize the progress in the synthesis and the biological activities of the peptide-based drug, along with some of the uses. We start with the historical aspect and key points in the development of the corresponding field. In general, the development part describes the approaches of peptides synthesis, design strategies, screening methods, and optimization for stability and bioavailability. We then describe the action of such mechanisms as with respect to receptors, enzymes, and peptides that can penetrate cells. It has also expanded the assessment of the description of peptide drugs in the treatment of cancer, cardiovascular diseases, metabolic diseases, neurological diseases, infectious diseases, and immunotherapy. We cover both the problems in the formation of peptide drugs like stability, delivery, and regulatory issues and the opportunities like nanotechnology, bioprinting, and CRISPR. Last, we discuss the outlook of the peptide-based therapeutics and review features, which are promising for the development of new trends and perspectives of application. The present review is intended to give an up-to-date and easy to grasp information regarding the status and perspectives of peptide-associated medicines in contemporary pharmacology.

Keywords- Peptide Therapeutics, Drug Development, Peptide Stability, Targeted Therapy, Clinical Applications.

I. INTRODUCTION

Over the past years, peptide-based drugs have gained importance as one of the most potential therapeutic agents unique in comparison with regular small-molecule drugs [2] [3] [4]. They show relatively high binding selectivity and low cytotoxicity, and therefore there is a potential for a broad spectrum of medicinal uses [2]. There has been advancement in recombinant and synthetic methods that have opened up new vistas for the creation of new therapeutic proteins and peptides [2]. A brief comparative account of the characteristics of therapeutic proteins and peptides as opposed to traditionally developed small molecule drugs would be the following. They possess better specificity, higher activity and they induce less toxicity because they cause an immune reaction when administered into the body [5]. Still, therapeutic proteins and peptides are an interesting field; on the one hand, their structure predisposes them to many problems that are difficult to avoid when using the protein-forming approach, namely, large molecular weight, variability of the surface charge, and physical and chemical instability of the tertiary structure of the peptide chain, which hinders its standalone delivery into the intracellular space and its ability to cross the cell membrane [5]. To address these issues, the opportunities of employing such innovative approaches and significant topic as the use of polymeric nanostructures for targeted delivery and increasing of the therapeutic potential of the peptide-based drugs were under investigation [6].

II. HISTORICAL PERSPECTIVE

Peptide-based drugs are still a relatively young class of drugs that have a rather vast and filled with experiments and discoveries history. After discovery of insulin in 1921, peptides became significant therapeutic entities with carving out various usage like antimicrobial, antiviral, anti-tumor, and anti-inflammatory etc. [7]. The selectivity arising from receptor-ligand binding of

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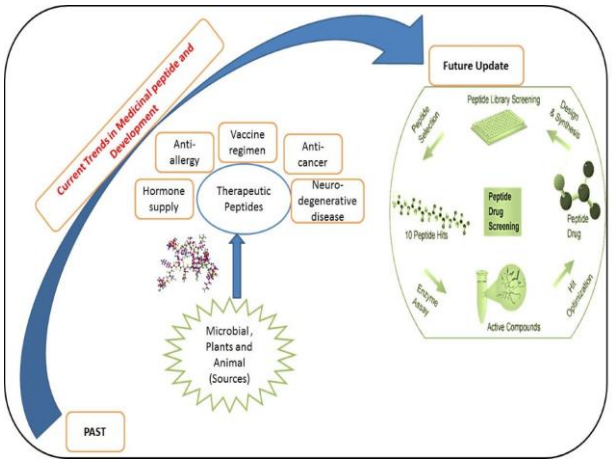
peptide drugs explain why they are powerful and have low toxicity prerogatives, with more than 70 approved peptide drugs in significant markets [8]. The synthesis and production of the peptide drugs has also evolved over the period of time with concern to the stability, bioavailability and cellular uptake of the drugs. Bar one traditional method, which focuses on the use of a chemical library, other methods of preparation include the use of bioinformatics tools, computational techniques, and efficient synthesis methods in the design of superior products with increased efficacy and biodegradation [7]. The constant updates into today's option of peptide therapeutics have also broadened into new horizons in medicinal chemistry that render peptides fairly beneficial in innumerable medical specialties [8].

III. ADVANCEMENTS IN THE FORMULATED PEPTIDE BASED DRUGS

Cationic peptides have been initially developed with a relatively simple structure; however, the current cationic peptide based drugs are more optimized in design. From natural royalties, peptides have been chemically modified in ways such as side-chain changes, cyclization, along with conjugation with heterocycles to enhance their therapeutic activities [7]. The uses of peptides are numerous due to their characteristics, including high selectivity, low side effects, and different pharmacological effects [9]. To overcome the problems such as instability, short T½, several approaches such as lipidization of peptides have been sought thus influencing the pharmacokinetics' and bioavailability of the peptide drugs[10]. Peptides have been applied in courses such as antimicrobial, antiviral, anti-tumor, and anti-inflammatory, hence the flexibility of peptides in modern medication [7]. The synthesis of peptides have improved over the years especially through avid usage of bioinformatics and computational study thus enhancing the role of peptides as promising entities in the pharmaceutical industry [7].



3. 1 Synthesis and Design

The trends in the synthesis and design of the peptide-based drugs have grown through the phase in respond to the problems like; stability, bioavailability and selectivity of the drugs [9]. First, there are certain problems associated with peptide-based biologics since they have low selectivity and stability, and were rapidly degraded in the body; however, now many new trends have appeared, including the creation of new antagonists and agonists that are conjugated with peptide therapeutics along with drug carriers, especially in anticancer treatment, and have high target selectivity and minimal toxicity [11].

The historical development of targeted peptide drugs comprises of synthesis and design of peptides, peptides' stability, peptides' bioavailability and cell membrane penetration issues to yield selective and effective peptide drugs for various physiological roles [9]. The peptide-based drugs are made through molecular modeling and design for the specific treatment of cancer involving peptide-drug conjugates, nanocarriers, and prodrugs. Newly emerged peptide–drug conjugates (PDC), peptide-based nanocarriers and prodrugs may be possibly considered as an ideal treatment regimen for patients and contribute valuable information in reasonable drug design and production for the future pharmaceutical industry [11].

Peptide design also comprises iterative optimization which utilizes Rosetta software for the creation of new peptides that target proteins and may further the cause of peptide based drug design by way of computers in a generalized form, an overview of the design of a novel peptide is given, which can be utilized in a loop to optimize and select new peptide sequences in relation to a certain protein, and an. xml interface is utilised to place the functions for repeatable performance [12]. In recent years, structure and design of the peptide-based drugs involve the rationale ways to manage the vast chemical structure space and allow for the proper molecule construction with an assurance of its effectiveness, handled thorough the structure prediction and molecular dynamics simulations [13].

3.2 Vesicle Peptide Libraries and Screening

Peptide libraries are useful in research because they supply multiple peptides for different purposes in any research program. They allow a large number of motifs to be identified and evaluated for the description of multiple different x-mer peptides in the same N-mer peptide feature [14]. These libraries can hold peptides with non-canonical amino acids, which can serve as a protein binding agent in providing different, better, and more selective purposive for pharmaceutical uses.

Peptide libraries are compound libraries of diverse peptides used for screening out bioactive molecules which could possibly be theraputically used. In vitro and in silico HTPS technologies are equally efficient in searching for peptide compounds' high affinity and specificity [15] [16].

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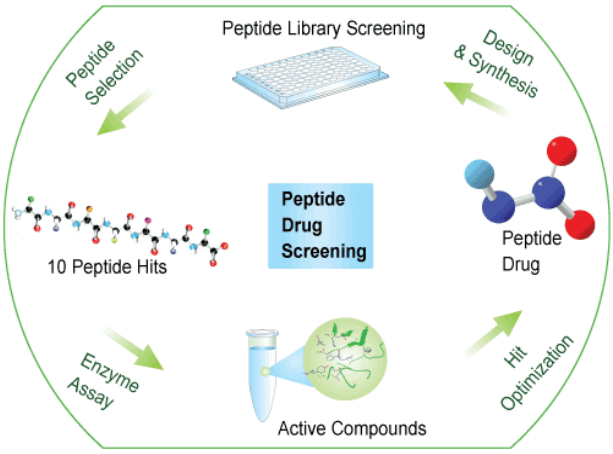
These libraries are crucial for identifying peptides that can affect protein-protein interactions, negate the effect of transcription factors, and have affinity for RNA.

Also, the sera cellulose-bound DNA-encoded peptide libraries in mammalian cells are used to get started with protein-evolutionary modification and functional peptide/antibody selection; this is important in the study of transmembrane proteins and human disease-related proteins [17].



3. 3 Optimization and modification

Peptide based drugs have been paid considerable attention because of their potential therapeutic uses while have some hurdle such as degradation and instability. Different optimization and modification techniques have been explored by researchers for improving the functionality of the peptide; these are the backbone modification, side-chain modification, incorporation of the amino acid substitution, and utilization of unnatural amino acid [18] [19] [7].

Peptide-based drug optimization requires structural change in ligand to improve selectivity and stability that is paramount in translation of these compounds to clinical uses in cancer targeted drug delivery, tumor diagnosing, etc [20]. Some of these are the increase in size, hydrodynamic diameter, and the negative charge as well as increasing plasma protein binding in order to decrease the rate of renal clearance and proteolytic degradation [21].

Enlightenment and alteration techniques of occurrence and property of peptide pharmaceuticals are important for defeating drawbacks like quick degradation, poor diffusion across the lipid bilayer membrane and low solubility in water [18]. These strategies include incorporation of unnatural amino acids, mutations of the backbone and side chains, and amino acid replacements with a view of improving the positions' stability and functionality [19] [20].

Such computational techniques like the mPARCE protocol help evolve iterative algorithms to give the best of the peptide sequences by doing single point mutations and approximating protein affinity through sampling of conformations [19]. Sorts of targets for peptide drug delivery are the increase in selectivity and stability of the applied molecules by in their structure modification and increasing target size, hydrodynamic diameter, negative charge, and plasma protein binding to prolong half-life and decrease clearance [20] [21]. These innovations in the modification and optimization of peptides will help herald newer forms of therapeutic peptides that are clinically far more effective and precise in targeting disease-associated pathways.

IV. MECHANISM OF ACTION

These drugs act by interacting with receptors and ligands making them have very selective actions [9]. These drugs have attracted much interest in a number of disease categories because of their capacities for delivering a drug, stimulating an immune reaction, and selectively attaching to a molecule [22].

The loss of protein's shape, for example, lactate dehydrogenase 5 (LDH5), can be prevented through peptides and thereby rendering the cancer killing effect into an attractive classifier and therapeutic target [23]. In the framework of viral infections, and with reference to coronaviruses in particular, peptides are considered as agents capable of interfering with various phases of the viral lifecycle [24].

Furthermore, enzyme-resistant GLP-1 peptide analogs have been proved to exhibit cardioprotective effects by influencing different signaling pathways associated with cardiac damage, oxidative stress, inflammation, and apoptosis; it shows that peptide-based drugs affect numerous aspects of disease in different sorts of ways [25].

4. 1 These are Receptor agonist and Receptor antagonist

Peptide based drugs work as an agonist or an antagonist because by binding with the receptors by receptor-ligand interactions the effects are highly selective [24] [9]. These peptides can thus imitate natural ligands; this is because they are smaller and have specific binding characteristics; they can actually destabilize functional complexes 26. For example, a series of enzyme-resistant GLP-1 peptide analogs acts as agonists that bind to GLP-1 receptors, allowing the prevention of cardiac injuries, decrease the inflammation level, and obtain cardioprotective effects [25]. Few peptides derived from microdomains of receptors including serpentine type have been useful to control hormone signal systems as selective agonist or antagonist; they allow the determination of receptor-ligand coupling or interference with autoimmune reactions, and serve as functional probe in physiology-pathophysiology [27]. In turn, the treatment based on peptides sharply changes the agonistic or antagonistic action only with definite receptors, destroys functional complexes, and controls signal systems.

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4. 2 Enzyme inhibitors

Over the course of years, the peptides inhibitors have been identified as the potential therapeutic agents to modulate the enzyme activity. These inhibitors obtained from above mentioned strategies including rational design, combinatorial peptide-display technologies, and constrained peptides have been known to be active against enzymes like metalloproteinases (from ADAM and ADAMTS families)[28], serine proteases [29] and protein-protein interactions (PPIs)[30] [31].

Strengthen of this approach are; specificity, which involves generation of potent inhibitory effect comparable to that of a monoclonal antibody, and potential to increase the plasma half-life and bioavailability that makes them suitable for clinical application. Peptides also have functioned as drugs by interacting with enzymes that participate in physiological and pathological processes and, therefore, can be seen as a well-equipped weapon in medicine people's hand against enzymes, as well as a new approach to effective enzyme inhibition and therapy.

4. 3 Cell penetrating peptides

CPPs are short peptides with the characteristic of delivering across cell membranes-CPPs are useful for drug delivery systems. The ways by which CPPs enter the cell include comes in contact with the lipid bilayer, where cationic peptides such as TAT48-60 and amphipathic peptides like MAP has been established to have strong electrostatic interaction with the cell membrane [32]. Also, the hydrophobic core part proven in Pep-7 is useful in trans-membrane processes, thus used in the delivery of therapeutic cargoes into cells [32]. CPPs have multipurpose to conjugate drugs, nucleic acids and proteins into cells for particular diseases like cancer, diabetes and viral diseases [33] [34] [35].

At the same time, some issues, such as non-tissue-specificity or suboptimal pharmacokinetics, have to be resolved to expand the application of challenges 4. In conclusion, based on the current understanding of CPPs and their ability to enable targeted drug delivery and treat a range of diseases, CPPs represent a viable approach for alleviating symptoms and improving patients' quality of life.

V. THERAPEUTIC APPLICATIONS

5. 1 Oncology

Peptide drugs have a significant application in oncology due to the observed pharmacological effects of differently used peptides. PRRT has been shown to provide good response in somatostatin receptor positive tumors with evaluation of overall response rate up to 30% and better quality of life and survival rate of the patients[36].

Cyclic peptides have also been used to treat hormone sensitive cancers like prostate and breast cancer using drugs like, goserelin acetate, leuprolide acetate, somatostatin and octreotide with showing anticancer effects [37]. Additionally, Pes have been synthesized for positron emission tomography and peptide receptor radiotherapy, in addendum, expanding the prospects of cancer diagnostic and therapeutic management[38].

Based on this information it is suggested that peptide-based drugs act upon cancer cells by several ways that are briefly discussed below; so, they could be used in cancer treatment. Peptides offer high selectivity, and low cytotoxicity and since these molecules can be synthesized to adhere to certain cell surface receptors and proteins that are overexpressed on cancer cells, they could be used to actively target the cancer cells [39] [40].

These peptides can also kill cancer cells by blocking cell signaling, shutting down the formation of new blood vessels to tumors, modulating the immune system , and preventing cancer cells from repairing their DNA [41]. Also, peptides are able to encapsulate cytotoxic substances or isotopes and transport them selectively to cancer cells for increased efficiency [39] [41].

Moreover, it is noteworthy that compounds derived from peptides can suppress metastatic progression by influencing such cell components as integrins and can potentially overcome the challenge of drugging some oncology targets, for instance, lactate dehydrogenase 5, by means of structural mimicking [23] [42]. Despite obtaining only decent results, peptide-based drugs are used to thwart the activity of LDH5 and subsequently kill breast cancer cells. This new method may prove to be a viable way of addressing cancer proteins that have been classified as being off-limits for drugs [23].

5. 2 Cardiovascular Diseases

Actually, it has been noted that peptides are important tools for targeting cardiovascular diseases because they are precise in their activity. The use of peptides has for example been found useful for site specifically administered treatment of heart pathologies including heart failure autonomics [43]. These drugs are comparatively new and can be considered as prospective for the treatment of CVDs because of the broad range of pharmacological effects and high selectivity [44]. Some of the peptides such as glucagon-like peptide-1 receptor (GLP1R) agonists exert vast cardio-protective characteristics through the mitigation of cardiac damage, attenuation of oxidative stress and the inhibition of cell death pathways in cases such as acute myocardial infarction (AMI) [25]. Also, eptifibatide, an antagonist of the glycoprotein IIb/IIIa receptor from the venom of the rattlesnake, has exhibited potency in combating platelet activation and coagulation; thus, it may have a prospect in treating CVDs such as ACS and myocardial infarction [45]. Peptide based supramolecular therapeutics or PST is a promising strategy to constructs nanomedicines to fight against multiple eminent diseases for its biocompatibility and bioactivity including the CVD's. It is, therefore, essential to foster the synthesis of peptide therapeutics for CVDs in view of the huge burden associated with these diseases worldwide [47].

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5. 3 Metabolic Disorders

Some of the registered peptide-based drugs are applicable for treatment of metabolic disorders: CHM-273S is a peptide separated from milk hydrolysate which has been proven to possess the ability to help treat obesity and kind 2 diabetes through enhancing the manifestation of IRS2 mRNA, leptin signaling employing STAT3, ameliorating glucose intolerance, as well as insulin resistance, and finally lowering body weight. Further, GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists have positive impacts on different aspects of the cardiometabolic spectrum regarding obesity, metabolic syndrome type 2 diabetes, and related disorders like NAFLD/NASH through speckle effect, insulin stimulating effect in glucose induced glucagon suppression and useful cardio-renal effects [48].

There is a increasing focus on the opportunity of utilizing these peptide based therapies for managing metabolic disorders because of high evidence that androgen receptor directly influence pathways associated with glucose homeostasis, energy expenditure, and inflammation therefore expanding the potential therapeutic targets in the scope of metabolic diseases.

5. 4 Neurological Disorder

There is hope in peptide therapeutics for neurologic disorders, which can address molecular mechanisms of diseases in Alzheimer's and Parkinson's [49] [50]

These bioactive peptides can bind to amyloid-beta which is a principal component causing Alzheimer's disease, decrease inflammation, regulate the effects of neurotransmitters, and enhance cognitive abilities [50]. Although conventional development of small-molecule drugs for CNS diseases is accompanied by relatively high rates of failure, peptide-based medicine is just emerging as a more suitable option, provided the recent progress in the development of nose-to-brain delivery techniques [51].

Molecules such as erythropoietin, glucagon like peptide 1 and oxytocin have been found to have neuroprotection based on the activation of cellular and molecular processes in neurodegenerative diseases [52]. Nevertheless, hurdle likes blood brain barrier, the peptide drugs based on the neuropeptide has the future of overcoming all the demerits of present methods of treatment of neurological disorders [53].

Furthermore, modality of peptide therapeutics is being covered to overcome the shortcomings of drug-like molecules for the CNS disorders ranging from neurodevelopmental disorders, brain injuries, stroke, and neuropsychiatric illnesses are being developed [51]. Future studies focusing on the ways of improving peptide choice, administration, and comprehending their operation are necessary for creating the required funding therapies for changing the outcomes of severe neurological diseases.

5. 5 Infectious Diseases

AMPs and AVPs have come out to be very effective in the treatment of diseases arising from drug-resistant microbes as well as viral infections. AMPs, which are positively charged and contain both hydrophilic and hydrophobic parts, bind to bacterial cell membranes, and as a consequence, the microbial cells die [54]. Some of the AVPs that have been used include influenza A virus, HIV and herpes simplex virus proving that they have antiviral capability [55]. Peptide drugs extracted from marine organisms have versatile bioactivities such as antimicrobial and antiviral properties and so have the potential to cure viral diseases [56].

The general goal of synthesizing peptidergic mimics of natural AMPs is the avoidance of such issues like toxicity and hemolytic activities in order to expand the therapeutic applicability of the presented compounds against drug-resistant microbes [54]. Some of the approaches, which are suggested to increase the efficiency of the utilization of AMPs and AVPs in clinical practice as well as to minimize their drawbacks, are the modification of the structures of some peptides, using nano technologies and undertaking clinical trials.

5. 6 Immunotherapy

Peptide based drugs increase the efficacies of immunotherapy through several ways. Peptides can activate immune cells, release immune responses for tumor immunotherapy, and regulate both the innate and adaptive immune cells, enhance the anti-tumor immune responses [60]. Three types of peptide vaccines act on tumor antigens: they stimulate the formation of antitumor T cells and, thus, overcome ''immunologic tolerance'' to tumor-associated antigens, which results in substantial antitumor effects [61] [62]. Therapeutic peptides can be enhanced by nanocarriers by the formation of nanostructures, suppression of tumor growth, and stimulation of immune responses for anticancer properties [63]. Biocompatible peptide based nanomaterials are able to self assemble into nanostructures and thus can be used as antigens, carriers as well as adjuvants in cancer immunotherapy, boosting immune response associated with safety [64]. Thus, the role of the peptide based drug cannot be emphasized enough in the enhancement of immunotherapy by targeting the tumor associated antigens, in controlling of the immune responses and in the boosting of the therapeutic peptides and proteins.

These drug have come out to be potential candidates to be used in immunotherapy of cancer by leveraging TAAs or TSA of cancer cells to elicit immune responses[61] [65]. Many of these peptides can bind to immune cells and promote anti-tumor immune responses while also overcoming the biological barriers to deliver the correct form and amount [6]. However, there are certain drawbacks associated with peptide vaccines for instance low immunogenicity, because of this the immunosuppressive tumor microenvironment inhibits

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the effectiveness of peptide vaccines in clinical trials [65]. Identification of peptide epitopes is helpful to orient on immune reactions to therapeutic drugs and to contribute to the improvement of effective treatments for refractory patients [67]. Due to the self-assembly ability of peptides and the ability of peptides to functionalize the nanocarriers, peptide-based drugs holds promise in boosting the effectiveness of cancer immunotherapies and may augment with immune checkpoint inhibitors and chemotherapy [61 66].

Area	Mechanism of Action	Examples	Challenges	Potential
Oncology	Targeting cancer cells, inducing cell death, delivering payloads, suppressing metastasis	PRRT, cyclic peptides, PET/PRRT peptides	Limited efficacy, drug resistance	Broad targeting, high selectivity
Cardiovascular Diseases (CVDs)	Site-specific treatment, cardio-protection, inhibiting platelet activation	GLP-1R agonists, eptifibatide, PST nanomedicines	-	Broad effects, high selectivity, addressing CVD burden
Metabolic Disorders	Improving glucose metabolism, reducing obesity, addressing metabolic syndrome	CHM-273S, GLP-1R agonists, dual GIP/GLP-1R agonists	-	Targeting androgen receptors for expanded options
Neurological Disorders	Addressing disease mechanisms, reducing inflammation, regulating neurotransmitters, neuroprotection	-	Blood-brain barrier	Advantages over small molecules, addressing various disorders
Infectious Diseases	Disrupting microbial membranes	AMPs, AVPs	Toxicity, hemolytic activities	Addressing drug resistance, expanding applications
Immunotherapy	Activating immune cells, overcoming immune tolerance, enhancing delivery/efficacy	Peptide vaccines, peptide-based nanomaterials	Low immunogenicity, immunosuppressive tumor microenvironment	Improving immunotherapy effectiveness, combining with other therapies

VI. THIS ARTICLE DISCUSS SOME THE CHALLENGES THAT ARE LIKELY TO AFFECT PEPTIDE DRUG DEVELOPMENT

6. 1 Stability and Degradation

Peptides are addressed by issues related to stability and degradation during drug development affecting their ability to function as treatment agents. Several challenges are inherent in the form of degradation pathways including aggregation, deamidation, hydrolysis, β-elimination, disulphide exchange and the like. As a result, common techniques of peptide stabilization are the choice of a suitable buffer, pH levels, deterioration prevention by antioxidants/preservatives, divalent metal ions, light and low temperature [68]. Protein-protein interactions are the most challenging targets for traditional drug discovery because they were considered undruggable, but with the help of PROTACs based on peptides, many diseases can be treated [69]. This is through structural changes and adjustments and new delivery strategies; cell-penetrating peptides and stapled modified peptides to enhance the stability of the peptide against the degradative pathways of enzymes [70]. Furthermore, stability of the gut is still a major problem for peptides in oral formulation and most of the peptide drugs are degraded in the gastrointestinal tract; however, cyclotides proved to be resistance to this degradation and emphasizes the need of establishing standardized conditions for evaluation of stability of peptides in the gut [71].

The major stabilities factors for peptides in drug include those that belong to the peptide drugs, such as peptide sequence, concentration, pH, charge, and outside factors such as excipients, chemical degradation, surfaces, and interface [72]. Proteins and peptides are easily degraded by the enzymes in the gastrointestinal track which remains a major challenge in oral peptide drug delivery [71]. Possible approaches to enhance the stability of peptides includes N and/or terminal blocking or changing, D-form of the amino acid or incorporation of non natural amino acid, cyclization, alteration of the backbone, peptide-particle system, and increase molecular weight [73]). Moreover, molecular design strategies such as cyclization and D-amino acid incorporation are point that contribute to diminution of degradation, and passive permeability of peptide drugs,

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principally in the colon region which is beneficial targeted region in IBD and CRC. [74] Knowing these stability factors is critical for the development and application of peptide therapeutics.

6. 2 Delivery Methods

There are difficulties in applying peptide-based drugs orally because such medication has enzymatic susceptibilities and poor permeability; therefore, it tends to be given parenterally [75] [76]. To improve the issue of poor OBA, there has been a consideration of several systems like nanoparticle carriers, enzyme inhibitors, mucoadhesive polymers, and chemical modifications of peptide structures [75] [77].

Approaches such as nanoparticles, transport, channels, hydrogels, microneedles, and proteolytic enzyme inhibitors have been discussed to improve the enteral delivery of peptide and protein drugs [75].

Moreover, naturally sourced polymers such as chitosan, starch and cellulose is being researched to be used as the carrier in the nano system delivery to enhance the effectivity in delivery of drugs particularly peptides and proteins [78]. These new developments involve improved systems of delivering peptides which seeks to address the problems faced with the delivery of peptide-containing drugs and significantly increase the application of peptides in medicine.

Peptide-based drugs are among the drug categories that have experienced improved in ways of delivery for optimized effectiveness and presence in the body fluids. Some Recent strategies are as follows: Nanoparticles and liposomes [75], Nanopolymers [76], CPPs [77], Microneedles [78], [79].

CPPs have recently been identified to be effective cell-penetrating molecules, which can overcome issues such as poor solubility and landing of the drug in the wrong place [80]. All these peptides have been established to exhibit exceptional delivery performance and thus hold efficacy on various types of drugs, biological challenges and targeting effectiveness [81]. Further, the peptide based systems has been employed for gene delivery in combined drug delivery systems that demonstrate the possibility of multiple functional antitumor therapy [82]. In conclusion, these innovations summarise the various and progressive delivery platforms for peptide related therapeutics with the vision to transform the height of tailored medication system in healthcare.

6. 3 Risks and Issues of Regulations and Manufacturing

6. 3. 1 Challenges facing the peptides and proteins based therapies.

Challenges that come with the use of peptide-based therapeutics include; safety, efficacy and quality of the products as has been documented in various papers. The interaction of showing understandable risk constraints and establishing control over the quality of drug substances for oral peptide drugs is underlined, and the production processes need to be validated according to the principles of GMP [83]. Also, special regulatory requirements for drug-drug interaction evaluation in therapeutic peptides are undefined, which creates uncertainties during the drug development process; thus, it requires risk-based approach and harmonization across the industry [84]. Lack of harmonization in the evaluation of the synthesis of existing regulatory guidances on synthetic and conjugated peptide assets has posed difficulties to both the regulators and sponsors, hence the need to achieve uniformity in the determination of assets regulatory categories and guidelines [85]. Nevertheless, considering the recent expansion of the application of peptide therapeutics in different therapeutic fields, it is necessary to mention the need to mitigate regulatory issues to enhance patient protection and facilitate the development of peptide drugs [79] [86].

6. 3. 2 Manufacturing as a process and its challenges and possibilities.

The process of manufacturing peptide-based drugs is quite challenging and complicated and thus needs a new approach to deal with. Some standard methods include solid-phase peptide synthesis (SPPS) and liquid-phase peptide synthesis (LPPS) out of which SPPS is typically preferred more because of its effectiveness [87]. However, SPPS is not a very environmentally benign method due to its very high PMI, thus the need to find a greener way to synthesize the compound [87]. Improvement of industrial-scale peptide synthesis and more specifically for synthetic peptides with a high market demand such as octreotide is essential to develop new strategies for peptide manufacture [88]. Also, the production of peptides and advancements in their delivery systems and formulations have made the therapeutic peptides one of the most appealing modalities in clinics as their targeting is accurate and they have higher bioavailability [79] [87] [89].

In summary, managing of manufacturing concerns by environmentally friendly and innovative strategies and technologies is crucial to the further development of the peptide-based drugs.

VII. MAIN DEVELOPMENT IN THE FIELD OF PEPTIDE DRUG DEVELOPMENT

7. 1. Nanotechnology and Peptide Delivery

Nanotechnology is one of the key in improving the peptide drug delivery, mainly with regard to solubility and permeability and increased stability [76] [90]. Nanoparticles with small particle size and suitable surface charge augment the bioavailability and stability of the peptides and peptidomimetics based therapeutics with the advantage of high bioreactivity and peptide drug design ability [46] [91].

Some of the nanoformulation techniques that have been very useful in solving challenges like degradation in the gastrointestinal tract and low permeability across the intestinal barrier have been

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nanoparticles, liposomes and polymers which have enhanced the oral bioavailability of peptide drugs [76] [79]. Using nanotechnology the researchers hope to come up with better drug delivery options that facilitate the delivery of the therapeutic agents to the specific sites where they are wanted with least side effects that can endanger the lives of the patients hence changing the face of personalized and precision medicine in the healthcare market [79] [91].

7. 2. Bioprinting and Personalized Medicine

7. 2. 1 The position the actual bioprinting regarding peptide therapeutics.

Bioprinting is very important for the fabrication of peptide therapeutics because the complex 3D structures can be released for tissue regeneration and wound healing through delivery of therapeutic peptides. P, e. g. , a pro-angiogenic QHREDGS peptide, can be added into the development of mentioned 3D-bioprinted patches to improve angiogenesis and tissue regeneration [92]. Controlled delivery of therapeutic proteins using of bioinks in 3D printing constructs also enhances cell migration and tissue regeneration through stimuli effective in the formation of new blood vessels [93]. Peptide-based bioprinting technologies in the fabrication of artificial tissue constructs have a possibility to promote biomimetic properties of the printed tissue since they align the control over the cell fate and tissue vascularization due to the formation of spatially defined cell-laden structures which resemble the native extracellular matrix [94]. Also, ultrashort self-assembling peptide hydrogels have been observed for muscle tissue development for muscle regeneration in 3D bio-printing [95]. Conformational versatility of self-assembling peptide inks in bioprinting enables the creation of dynamic structures of tissues in bioprinting facilitating enhanced regenerative medicine and tissue engineering [96].

7. 2. 2 Personalized peptide treatments.

Peptide treatments can be administered individually involving personalized peptide vaccination and neopeptide vaccines like EVX-01 and NeoVax in different types of terminal malignancies. There was enhanced immune response and survival effects in PPV for aCRC; cytokine levels and peptide-specific CMLs have been identified as indicators of survival [96]. , when used in metastatic melanoma as a backbone for anti-PD-1 treatment, elicited neoantigen-specific T cells and displayed objective tumor responses in more than 30% of patients [97]. Likewise, NeoVax in glioblastoma patients boosted neoantigen-specific effector T cells suggesting that design of cancer vaccines to include multisector sampling needs to be incorporated for clinically good results [98]. These customized peptide therapies portray the prospect of immunotherapy to bolster the antitumor immunity and should be examined in larger clinical trials for the improved patient survival.

7. 3. CRISPR and Gene Editing

Apart from speeding up the discovery of new peptide-based treatment, the application of CRISPR technology in drug development rappels for the need policy makers and ethicists to pay attention to how best to incorporate such ethical issues in the processes of developing and distributing new drugs [99] The ability to perform precise modifications of DNA sequences has been made possible by CRISPR-Cas systems that offer a promising utility of curing genetic diseases [10] Scientists are studying the impressive Crispr Cas9 that could be employed for an alteration of the genes of the peptide drugs in an effort to improve the therapeutic effect offered. Thus, besides gene editing through utilizing CRISPR-Cas9, there are other methods such as using peptide nucleic acids (PNAs) which can silence genes and be used in therapeutics [101]. Further, researchers' efforts have been focused on the application of combined amphipathic membrane-permeable peptides such as LAH5 to deliver CRISPR-Cas9 components including the positive control of gene editing and HDR-mediated gene correction in many cell types[102] [103]. These advancements bring into focus that genomic engineering is not stagnant in its technological advancement but is open to new horizons of knowledge for targeting the disease genes by designing new peptide-based drugs using CRISPR mediated gene editing techniques.

Development	Description	Impact
Nanotechnology and Peptide Delivery	Using nanoparticles to improve peptide solubility, permeability, and stability	Enhanced bioavailability, targeted delivery, reduced side effects
Bioprinting and Personalized Medicine	Creating 3D structures for tissue regeneration and wound healing using peptide-laden bioinks	Personalized treatments, improved tissue regeneration
CRISPR and Gene Editing	Modifying peptide drug genes using CRISPR-Cas9 and other techniques	Potential for curing genetic diseases, developing new peptide-based drugs

VIII. FUTURE DIRECTIONS AND PROSPECTS

Thus, new trends in the development of peptide drugs are as follows: Peptides being used for targeting of still debated protein-protein interaction interfaces, given the structural versatility and solidity of peptides. Recent developments in the peptide design method, peptide synthesis method and peptide delivery system has impressed the efficiency of peptide drugs in treating many diseases and new breakthroughs in the future. In evaluating secondary structure, it is suggested that there are guidelines on the quality assessment of peptide drugs

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that derives from the standardization of evaluation on the high manufacturing quality [106]. Contributions from the integration of AlphaFold and Artificial Intelligence (AI) have created the possibilities of efficient prediction of the peptide-protein structures and promotion of the computational drug discovery engines in addition to providing new understandings of the binding mechanisms employing physics-based approaches including docking and molecular dynamic simulations [107]. As a whole, all of these trends want to solve the problems related to the discovery of peptide drug, enhance the selectivity for peptides, and renew the healthcare system of the patients based on the principles of personalised and precision medicine.

It is most expected that more advancements and innovations in the near future will be witnessed in peptide drugs due to the development in the field of peptide design and synthesis methods as well as the approaches towards the delivery of the peptide drugs. Peptides provide high specificities and affinity and the approaches like structure-activity relationship, molecular modeling will add to this specificity [79]. AlphaFold and Artificial Intelligence are some of the breakthroughs that can help in gaining an efficient prediction of the structures of peptide-protein and rebuild the drug discovery process[107]. Most restrictions have been addressed by new chemical modifications, such as side-chain modifications and cyclization to attain therapeutic peptides [7] [18]. To enhance the status of peptides together with their approachability; lipidization and other measures are in use and better drugs are being developed[108]. It can be noted that the synergy of AI and physics-based techniques may contribute to new findings in reformation of the peptide-based drug discovery and contribute to tailoring appropriate solutions for various complicated medical issues in personalized and precision medicine [107].

IX. CONCLUSION

Peptide drugs are a relatively emerging sector in terms of chemical entities, which is quite promising for further development because of specificity of action, efficiency, and relative multitalentedness. This review focuses on the achievement of a great deal in the discovery, refinement and usage of such therapeutics in many areas of medicine. Nevertheless, thanks to the further progress in technology and the appearance of new concepts, future branches of peptide-based treatments might eliminate the mentioned problems as stability, delivery, and so forth.

Enhanced prospects in PTD-Development are possible in individualized medicine, modern approaches to drug delivery, and new therapeutic groups of peptides. The future improvement is most likely to depend on further scientific investigation and industrial and clinical development alongside with the regulatory agencies. In the future, drugs based on peptides will be essential for addressing patients' neeeds and enhancing the quality of their lives in various clinical scenarios.

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