Development of Peptide Biopharmaceuticals

Subjects: Pharmacology & Pharmacy

Contributor: Vladislav Deigin , Yuri Poluektov , , Sergey Kozin

Peptides are low-molecular-weight substances that participate in numerous important physiological functions, such as human growth and development, stress, regulation of the emotional state, sexual behavior, and immune responses. Their mechanisms of action are based on receptor–ligand interactions, which result in highly selective effects. These properties and low toxicity enable them to be considered potent drugs. Peptide preparations became possible at the beginning of the 20th century after a method was developed for selectively synthesizing peptides; however, after synthesis of the first peptide drugs, several issues related to increasing the stability, bioavailability, half-life, and ability to move across cell membranes remain unresolved.

peptide synthesis peptide manufacturing peptide drug

1. Introduction

Studies of the chemical structures and biological properties of peptides and proteins became possible at the beginning of the 20th century, when Fischer [1] and colleagues developed a method for selectively synthesizing peptides comprising several amino acids. The use of peptides as drugs has evolved and continued to develop, and the molecular characteristics and structures of receptors for many important endogenous peptides have been identified [2][3]. In addition, the sequences of new peptide molecules have been determined, which can serve as a basis for identifying new peptide biomarkers of various diseases [4].

Currently, ~70 peptide-based drugs are registered in the international pharmaceutical industry [5], and 14 products are registered in the Russian Federation. The versatility of peptide functions in the human body has made it possible to create drugs (based on natural molecules and their modified analogs) that are approved for use in a wide range of indications from oncology to dentistry. Peptides that affect the functions of the central nervous system, including neurotransmitters and endogenous opioid peptides, have attracted the most interest.

2. Nomenclature, Classification, and the Roles of Endogenous Peptides

Peptides are mainly categorized in three different ways: (1) According to how many amino acids make up the chain (molecules comprising ≥50 amino acids linked together in chains by peptide bonds are called proteins, and shorter molecules are called peptides. Peptides are also subdivided into polypeptides (20–50 amino acids), oligopeptides (10–20 amino acids), and short or mini-peptides (2–0 amino acids)); (2) according to peptide source (plant, animal, or external (e.g., a marine source)); (3) or according to their functions in the human body [6][7][8][9]. For structure–

activity studies, peptides are often classified by their structures as linear peptides, cyclopeptides, multifunctional peptides, cell-penetrating peptides, or peptide–drug conjugates [10]. Additionally, classification is often made according to peptide physiological effects [11]. These divisions are somewhat arbitrary, and with the development of improved technological methods for generating proteins and peptides, the differences have gradually diminished.

Peptides represent a prime example of the functional diversity of a protein encoded by a single gene. For example, the insulin hormone processed in the body from proinsulin, as following cleavage of C-peptide [12], the proopiomelanocortin protein [13], forms the basis for various neuropeptides that interact with the opioid receptors μ, δ, and κ [14]. Many peptide hormones (i.e., vasopressin, prolactin, oxytocin, adrenocorticotropic hormone (ACTH), bradykinin, melanocyte-stimulating hormone, oxytocin, and glucagon) have synthesized as prohormones [15]. Neuropeptides comprise the most important class of endogenous peptides [16], are synthesized in the central and peripheral nervous systems, and help regulate most physiological processes.

In addition, endogenous peptides participate in regulating emotional states, sexual behavior, sleep, wakefulness [17], and immune responses [10][18]. Certain peptides promote the elimination of radionuclides and heavy metal salts from the body [8]. Many hormones (i.e., vasopressin, prolactin, oxytocin, ACTH, bradykinin, melanocyte-stimulating hormone, oxytocin, and glucagon) have a peptide nature [15].

3. Therapeutic Applications of Peptides

The strategies for using peptide drugs have shifted from hormonal therapy and diagnosing oncologic diseases towards treatments of a wide range of diseases, such as diabetes mellitus, osteoporosis, cardiovascular diseases, functional gastrointestinal diseases, and multiple sclerosis [10][11][19]. The current status of peptide drug development in different areas of the medicine is listed in **Figure 1** (THPdb: A database of FDA approved therapeutic peptides and proteins).

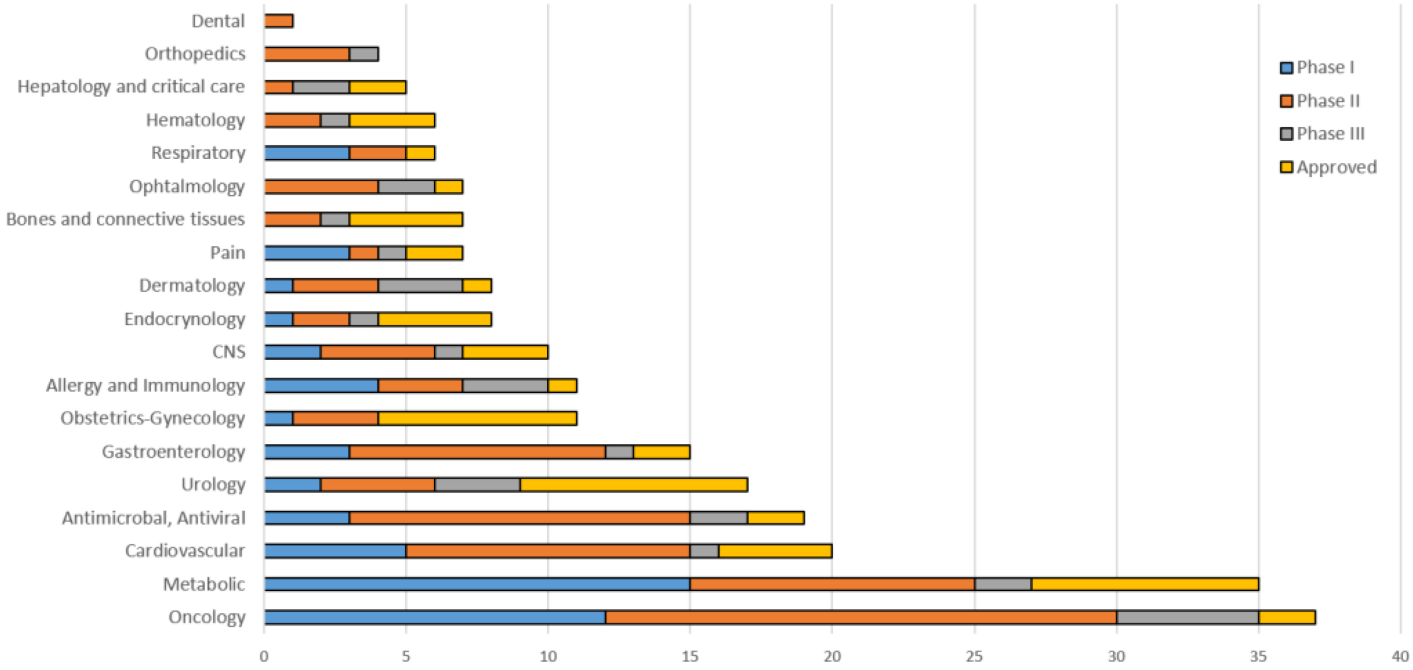

Figure 1. Peptides approved and in active development by therapeutic area.

In particular, growing interest exists in using natriuretic peptides as a novel non-invasive biomarker of heart failure and in developing stable forms of neuropeptides that would enable their use as potent medicines [20]. Neuropeptides are considered biomarkers or drugs for diseases associated with impaired regulation of energy balance, food–behavioral reactions, and mental disorders. Enkephalins and their derivatives are considered candidates for treating chronic pain, maladjustment, and pathological stress responses [21]. Neuropeptide Y is a prospective molecule for treating various diseases of the central nervous system, cardiovascular and endocrine systems, and respiratory and gastrointestinal tracts [22].

Pharmacological analogs of somatostatin are increasingly being used to treat cancer, acute pancreatitis, and acromegaly [23]. Diagnostic and treatment approaches that target cholecystokinin, such as receptor scintigraphy and radiopharmaceuticals, have been used in tumor imaging and/or therapy in vitro, in vivo, and in clinical studies [24]. Pharmacological analogs of cholecystokinin have been studied for applications in oncology, addiction, and eating disorders. Additionally, the presence of intestinal peptide receptors in immune cells and vagus nerve endings opens up new targets for pharmacological approaches for addressing aging and mental disorders [25]. Moreover, studies on treating neurodegenerative diseases using peptides have also been conducted [26]. Furthermore, bacteriocins are considered promising agents for treating antibiotic resistant strains of pathogenic bacteria, human defensins are being studied as antibacterial drugs [27][28], and many peptides are being evaluated as potential therapeutic agents in oncology research [19].

4. Problems Associated with Manufacturing Synthetic Peptides

Synthetic peptide drugs entered the global pharmaceutical market in the 1960s, and modern technologies enable the isolation and assessment of animal and plant peptides, as well as antimicrobial peptides from amphibians and microorganisms, as candidate therapeutic agents [29]. Nevertheless, most peptide preparations (~85%) are obtained by chemical synthesis, and only 15% are obtained by recombinant methods. Furthermore, chemical-synthesis technologies also provide opportunities to modify peptides using non-natural amino acids and introduce pseudopeptide bonds and other modifications not available using recombinant techniques [30].

Of the small-molecule chemicals prevailing in the global pharmaceutical market (85%), peptides represent only a small portion (2%) of the world drug market. However, the market for peptide- and protein-based drugs is growing approximately twice as rapidly as the rest of the drug market, indicating that peptides may soon occupy a more significant niche [11][31]. During the initial stages of peptide pharmaceutical development, a scarcity of registered peptide drugs was caused by several objective factors [32], including high production costs, low bioavailability when taken orally, insufficient stability, an insufficient ability to traverse cell membranes, and short half-lives. However, the advantages of peptide molecules include a high selectivity and affinity for the corresponding receptor, low toxicity and immunogenicity, as well as multiple biological targets in the body and a low likelihood of cross-interactions with other drugs.

In the previous 15 years, new synthesis strategies have emerged to enable changes in the pharmacokinetic properties and specificity of peptide molecules by modifying amino acids or the peptide chain, incorporating non-natural amino acids, conjugating peptides with carriers that increase the half-life, and/or improving peptide solubility. In addition, new targeted drug-delivery strategies have enhanced the stability and other physical and chemical properties of potential peptide drugs [11].

5. The Main Strategies for Developing the Next Generation of Peptide Drugs

The approaches used to increase peptide stability are continuously being improved, leading to new kinds of structural modifications [33][34]. One apparent solution for stabilizing the hydrolytic lability of drugs containing natural peptides is to incorporate modified analogs of natural peptides previously registered as parenteral drugs. Analog modifications are based on introducing substitutions in various parts of the original molecule in order to stabilize and sometimes change its structure, spectrum, and even direction of action [35].

An essential requirement for improving peptide structure is an ability to minimize the possible toxicity of the obtained analogs. Currently, many laboratories [36] are developing peptide-modification strategies to increase the binding affinity to receptors or active centers of enzymes, as well as their absorption, distribution, metabolism, and excretion profile (known as the “ADME” profile) [37].

Novel synthetic strategies allow for modulating pharmacokinetic properties and target specificity through amino acid or backbone modification by incorporating non-natural amino acids and conjugating moieties that extend half-life or improve solubility. Substituting natural amino acids is one strategy used to prevent hydrolysis, where

modifications are introduced at sites that undergo hydrolysis, followed by replacing the original amino acid [3]. The substituents can be d-amino acids, β-amino acids, dehydroamino acids, and various olefin derivatives. Such modifications improve the stability and increase the half-life of the peptide molecules in plasma [11][38]. Various critical issues associated with therapeutic peptide delivery have drawn increasing attention to the development of new formulations for alternative routes of administration, such as oral, nasal, buccal, pulmonary, transdermal, rectal, and ocular [39]. Penetration of drugs through oral mucosa into the systemic circulation is a major hindrance in their absorption, as the oral route easily degrades a hydrophilic, large-molecular-weight drug (e.g., proteins and peptides), resulting in their decreased availability in systemic circulation [40].

Examples of modifications include the introduction of proline and hydroxyproline (both resistant to protease degradation) into cleavage sites to replace easily hydrolyzed amino acids in order to improve in vivo drug stability [41][42]. In addition, N-methylation or the introduction of N-methyl-amino acids has also been used to increase peptide stability, reduce possible hydrogen bonding, and improve permeability [43]. Moreover, the simultaneous inclusion of d-amino acids and N-methylation at amide bonds can significantly increase metabolic stability, thereby creating additional steric hindrance. Furthermore, many structural modifications, including N-alkylation, can increase the biological and metabolic stability of peptides [44][45].

Proteolytic enzymes in the blood, plasma, liver, or kidney include exopeptidases, aminopeptidases, and carboxypeptidases, which hydrolyze peptide sequences from N- and C-termini. Therefore, N-acylation and C-amidation can potentially increase the resistance of modified peptides to proteolysis [46]. Linear cyclization is a generally accepted method of increasing protein rigidity, with this process resulting in the formation of intramolecular hydrogen bonds and decreasing intermolecular hydration. Head-to-tail peptide cyclization offers the advantage of strengthening the peptide chain, stabilizing the conformation, and inhibiting cleavage by endopeptidases. Therefore, cyclization might represent the simplest method to prolong the half-life of a peptide in vivo, as it often increases the biological activity of a peptide [35]. Moreover, introducing N-terminal d-amino acids can suppress degradation by exopeptidases, similar to reducing C-terminal carboxyl groups into a corresponding alcohol moiety [47].

The chemical “stapling” of amino acid side chains onto a peptide chain can be achieved via the insertion of residues into a peptide chain through hydrocarbon “inserts” or by forming lactam bridges to stabilize peptide helicity and increase their stability and intracellular permeability. The so-called “stapled-peptides” method is gaining popularity [48][49]. Another modern approach to increasing peptide stability and creating a more durable compound is to conjugate peptides with macromolecules. Various polymers have been applied for these purposes, including polyethylene glycol (PEG) [50] and polyvinylpyrrolidone, as well as the use of protein carriers, such as albumin. PEGylating peptides can effectively reduce their potential immunogenicity, maintain their biological activity, and slow down enzymatic hydrolysis [51]. In addition, some fatty acids are used to stabilize peptides and protect them against proteolysis. Peptide molecules are encapsulated into liposomes, nano/microparticles, or micelles with a higher molecular weight [52] to increase the half-lives and bioavailabilities of peptide drugs [53].

Conjugating peptides with lipids confer lipopeptide derivatives with new structural and biological properties that result in compounds with improved potency and selectivity. Lipidation of peptides leads to the formation of amphiphilic peptide conjugates with increased bioavailabilities and increased capability to cross cell membranes [54]. Recently, a new concept for creating full-length enantiomeric d-peptides, which involves replacing all l-amino acids with the corresponding d-amino acids, has become widespread, with such peptides (d-peptides) showing significantly improved stabilities and half-lives [55][56].

One of the first natural peptides to be successfully modified was the hormone vasopressin, which contains l-Arg and has a half-life in humans of 10 to 35 min [57]. Vasopressin analogs containing d-Arg instead of l-Arg are called desmopressin and have a half-life of ~4 h [58]. An analog of somatostatin (the drug octreotide, which is used to treat gastrointestinal tumors) has a shorter sequence than somatostatin (8 amino acids instead of 14) and l-amino acid substitutions for the corresponding d-amino acids[59].

The minimal cyclic structures of peptide compounds are 2,5-diketopiperazines (DKPs), which are cyclodipeptides obtained by condensing two α-amino acids.

Numerous different structures can be generated based on DKP in order to search for new lead compounds [60]. DKP derivatives are often found in nature both in the form of simple unsubstituted 2,5-DKP structures and more complex molecular structures in natural products, fungi, bacteria, plants, and mammals. For example, many antibiotics are DKP derivatives [61]. Drugs have been developed with structures ranging from simple cyclic dipeptides, such as derivatives of cycloserine dimers [62] or kairomycin B [63], to complex conjugated polynuclear systems, such as bicyclomycin [64].

2,5-DKP is resistant to proteolysis and an attractive target for structural and functional studies aimed at searching for new potential drugs. These conformationally limited chiral centroids have six positions available for structural modification by various functional groups with specific stereochemistry. The 2,5-DKP structure enables alterations at all six positions and stereochemical isomerization at all four positions of the optical centers. In addition, 2,5-DKP has a rigid framework that can mimic the preferred conformation by limiting the mobility of amino acids embedded in its structure. The 2,5-DKP structure comprises trifunctional amino acids containing various functional groups, which can be used to identify target positions with which this molecule interacts and to serve as linkers for attaching multiple functional groups (pharmacophores).

Pharmacophores should be able to easily undergo metabolic transformations, such as ester bond formation with the centroid and easy hydrolysis in the body. 2,5-DKPs are relatively easy to synthesize and can accommodate a wide variety of substituents (i.e., various amino acids used as building blocks). The large set of substituents makes it possible to widely vary the physicochemical characteristics of the molecule, including its structure, size, shape, lipophilicity, dipole moment, electrostatic charge, and functional groups. This flexibility enables in silico modeling of analogs for directed library design [65].

When looking for new lead compounds, it is critical to not introduce changes in the centroid or substitutions in the attached groups that can lead to toxicity. One reason explaining the different physiological activities of drug stereoisomers is the differences in their penetration into an organism, which may be due to the structural features of 2,5-DKP, the properties of biological membranes (which are produced from optically active, asymmetric material), and the presence of transport systems that transport metabolites across membranes [66]. In one approach that utilizes 2,5-DKPs [67] (both short peptide analogs and versions containing “inserts” at different positions in the chain), the DKP moiety is positioned at the N- or C-terminal end of the molecule or within the peptide. The use of this approach has become widespread and can increase the hydrolytic stability and possibility of oral administration [68]. Furthermore, some derivatives of branched DKPs can exhibit hemostimulatory [69] and immunosuppressive properties [70], with one study demonstrating an acquisition of several new drugs based on 2,5-DKPs [65].

References

1. Fischer, E. Untersuchungen über Aminosäuren, Polypeptide und Proteïne (1899–1906): Manuldruck 1925; Springer: Berlin/Heidelberg, Germany, 2013.
2. Góngora-Benítez, M.; Tulla-Puche, J.; Albericio, F. Multifaceted roles of disulfide bonds. peptides as therapeutics. Chem. Rev. 2014, 114, 901–926.
3. Sun, L. Peptide-based drug development. Mod. Chem. Appl. 2013, 1, e103.
4. Moore, A. The big and small of drug discovery. Biotech versus pharma: Advantages and drawbacks in drug development. EMBO Rep. 2003, 4, 114–117.
5. Lau, J.L.; Dunn, M.K. Therapeutic peptides: Historical perspectives, current development trends, and future directions. Bioorg. Med. Chem. 2018, 26, 2700–2707.
6. Baig, M.H.; Ahmad, K.; Saeed, M.; Alharbi, A.M.; Barreto, G.E.; Ashraf, G.M.; Choi, I. Peptide based therapeutics and their use for the treatment of neurodegenerative and other diseases. Biomed. Pharmacother. 2018, 103, 574–581.
7. La Manna, S.; Di Natale, C.; Florio, D.; Marasco, D. Peptides as Therapeutic Agents for Inflammatory-Related Diseases. Int. J. Mol. Sci. 2018, 19, 2714.
8. Thundimadathil, J. Cancer Treatment Using Peptides: Current Therapies and Future Prospects. J. Amino Acids 2012, 2012, 967347.
9. Malonis, R.J.; Lai, J.R.; Vergnolle, O. Peptide-Based Vaccines: Current Progress and Future Challenges. Chem. Rev. 2019, 120, 3210–3229.
10. Henninot, A.; Collins, J.C.; Nuss, J.M. The Current State of Peptide Drug Discovery: Back to the Future? J. Med. Chem. 2018, 61, 1382–1414.

11. Fosgerau, K.; Hoffmann, T. Peptide therapeutics: Current status and future directions. Drug Discov. Today 2015, 20, 122–128.
12. Zaykov, A.N.; Mayer, J.P.; Dimarchi, R.D. Pursuit of a perfect insulin. Nat. Rev. Drug Discov. 2016, 15, 425–439.
13. Millington, G.W.M. The role of proopiomelanocortin (POMC) neurones in feeding behaviour. Nutr. Metab. 2007, 4, 18.
14. Ludwig, M. Are Neuropeptides Brain Hormones? J. Neuroendocrinol. 2011, 23, 381–382.
15. Catt, K.J.; Dufau, M.L. Basic concepts of the mechanism of action of peptide hormones. Biol. Reprod. 1976, 14, 1–15.
16. Harris, R.M.; Dijkstra, P.D.; Hofmann, H.A. Complex structural and regulatory evolution of the pro-opiomelanocortin gene family. Gen. Comp. Endocrinol. 2014, 195, 107–115.
17. Schulte, I.; Tammen, H.; Selle, H.; Schulz-Knappe, P. Peptides in body fluids and tissues as markers of disease. Exp. Rev. Mol. Diagn. 2005, 5, 145–157.
18. Deigin, V.I.; Semenets, T.N.; Zamulaeva, I.A.; Maliutina, Y.V.; Selivanova, E.I.; Saenko, A.S.; Semina, O.V. The effects of the EW dipeptide optical and chemical isomers on the CFU-S population in intact and irradiated mice. Int. Immunopharmacol. 2007, 7, 375–382.
19. Schulz-Knappe, P.; Schrader, M.; Zucht, H.-D. The peptidomics concept. Comb. Chem. 2005, 8, 697–704.
20. Pagel-Langenickel, I. Evolving role of natriuretic peptides from diagnostic tool to therapeutic modality. Adv. Exp. Med. Biol. 2018, 1067, 109–131.
21. Henry, M.S.; Gendron, L.; Tremblay, M.E.; Drolet, G. Enkephalins: Endogenous analgesics with an emerging role in stress resilience. Neural Plast. 2017, 2017, 1546125.
22. Shende, P.; Desai, D. Physiological and Therapeutic Roles of Neuropeptide Y on Biological Functions. Adv. Exp. Med. Biol. 2020, 1237, 37–47.
23. Mazziotti, G.; Mosca, A.; Frara, S.; Vitale, G.; Giustina, A. Somatostatin analogs in the treatment of neuroendocrine tumors: Current and emerging aspects. Exp. Opin. Pharmacother. 2017, 18, 1679–1689.
24. Zeng, Q.; Ou, L.; Wang, W.; Guo, D.Y. Gastrin, Cholecystokinin, Signaling, and Biological Activities in Cellular Processes. Front. Endocrinol. 2020, 11, 112.
25. Lach, G.; Schellekens, H.; Dinan, T.G.; Cryan, J.F. Anxiety, depression, and the microbiome: A role for gut peptides. Neurotherapeutic 2017, 15, 36–59.
26. Barykin, E.P.; Garifulina, A.I.; Tolstova, A.P.; Anashkina, A.A.; Adzhubei, A.A.; Mezentsev, Y.V.; Shelukhina, I.V.; Kozin, S.A.; Tsetlin, V.I.; Makarov, A.A. Tetrapeptide Ac-HAEE-NH2 Protects

α4β2 nAChR from Inhibition by Aβ. Int. J. Mol. Sci. 2020, 21, 6272.

27. Soltani, S.; Hammami, R.; Cotter, P.D.; Rebuffat, S.; Ben-Said, L.; Gaudreau, H.; Bedart, F.; Biron, E.; Drider, D.; Fliss, I. Bacteriocins as a new generation of antimicrobials: Toxicity aspects and regulations. FEMS Microbiol. Rev. 2020, 45, fuaa039.
28. Park, M.S.; Kim, J.I.; Lee, I.; Park, S.; Bae, J.-Y.; Park, M.-S. Towards the application of human defensins as antivirals. Biomol. Ther. 2018, 26, 242–254.
29. Moiola, M.; Memeo, M.G.; Quadrelli, P. Stapled peptides—A useful improvement for peptide-based drugs. Molecules 2019, 24, 3654.
30. Vlieghe, P.; Lisowski, V.; Martinez, J.; Khrestchatisky, M. Synthetic therapeutic peptides: Science and market. Drug Discov. 2010, 15, 40–56.
31. Peptide Therapeutics Market: Global Industry Trends, Share, Size, Growth, Opportunity and Forecast 2021–2026. Available online: https://www.imarcgroup.com/peptide-therapeutics-market (accessed on 16 December 2021).
32. Kaspar, A.A.; Reichert, J.M. Future directions for peptide therapeutics development. Drug Discov. 2013, 18, 807–817.
33. Agyei, D.; Ahmed, I.; Akram, Z.; Iqbal, M.N. Protein and peptide biopharmaceuticals: An overview. Protein Pept. Biopharm. Overv. 2017, 24, 94–101.
34. Agyei, D.; Danquah, M. Industrial-scale manufacturing of pharmaceutical-grade bioactive peptides. Biotechnol. Adv. 2011, 39, 272–277.
35. Muheem, A.; Shakeel, F.; Jahangir, M.A.; Anwar, M.; Mallick, N.; Jain, G.K.; Warsi, M.H.; Ahmad, F.J. A review on the strategies for oral delivery of proteins and peptides and their clinical perspectives. Saudi Pharm. J. 2016, 24, 413–428.
36. Brayden, D.J.; Mrsny, R.J. Oral peptide delivery: Prioritizing the leading technologies. Ther. Deliv. 2011, 2, 1567–1573.
37. Di, L. Strategic Approaches to Optimizing Peptide ADME Properties. AAPS J. 2015, 17, 134–143.
38. Ratnaparkhi, M.P.; Pandya, C.S.P. Peptides and proteins in pharmaceuticals. Int. J. Curr. Pharm. Res. 2011, 3, 1–9.
39. Park, K.; Kwon, I.C.; Park, K. Oral protein delivery: Current status and future prospect. React. Funct. Polym. 2011, 71, 280–287.
40. Antunes, F.; Andrade, F.; Ferreira, D.; Morck Nielsen, H.; Sarmento, B. Models to Predict Intestinal Absorption of Therapeutic Peptides and Proteins. Curr. Drug Metab. 2012, 14, 4–20.
41. Wöhr, T.; Wahl, F.; Nefzi, A.; Rohwedder, B.; Sato, T.; Sun, X.; Mutter, M. Pseudo-prolines as a solubilizing, structure-disrupting protection technique in peptide synthesis. J. Am. Chem. Soc.

1996, 118, 9218–9227.

42. Harris, P.W.R.; Kowalczyk, R.; Hay, D.L.; Brimble, M.A. A single pseudoproline and microwave solid phase peptide synthesis facilitates an efficient synthesis of human amylin 1–37. Int. J. Pept. Res. Ther. 2013, 19, 147–155.
43. Räder, A.F.B.; Reichart, F.; Weinmuller, M.; Kessler, H. Improving oral bioavailability of cyclic peptides by N-methylation. Bioorg. Med. Chem. 2018, 26, 2766–2773.
44. Munegumi, T. Hydrophobicity of peptides containing D-amino acids. Chem. Biodivers. 2010, 7, 1670–1679.
45. Ano, R.; Kimura, Y.; Shima, M.; Matsuno, R.; Ueno, T.; Akamatsu, M. Relationships between structure and high-throughput screening permeability of peptide derivatives and related compounds with artificial membranes: Application to prediction of Caco-2 cell permeability. Bioorg. Med. Chem. 2004, 12, 257–264.
46. Sato, A.; Viswanathan, M.; Kent, R.B.; Wood, C.R. Therapeutic peptides: Technological advances driving peptides into development. Curr. Opin. Biotechnol. 2006, 17, 638–642.
47. Diao, L.; Meibohm, B. Pharmacokinetics and pharmacokinetic–pharmacodynamic correlations of therapeutic peptides. Clin. Pharmacokinet. 2013, 52, 855–868.
48. Rand, A.C.; Leung, S.S.F.; Eng, H.; Rotter, C.J.; Sharma, R.; Kalgutkar, A.; Zhang, Y.; Varma, M.V.; Farley, K.A.; Khunte, B.; et al. Optimizing PK properties of cyclic peptides: The effect of side chain substitutions on permeability and clearance. Medchemcomm 2012, 3, 1282–1289.
49. Verdine, G.; Hilinski, G.J. Stapled peptides for intracellular drug targets. Methods Enzymol. 2012, 503, 3–33.
50. Jevševar, S.; Kunstelj, M.; Porekar, V.G. PEGylation of therapeutic proteins. Wiley Online Libr. 2010, 5, 113–128.
51. Werle, M.; Bernkop-Schnürch, A. Strategies to improve plasma half life time of peptide and protein drugs. Amino Acids 2006, 30, 351–367.
52. Liechty, W.B.; Kryscio, D.R.; Slaughter, B.V.; Peppas, N.A. Polymers for drug delivery systems. Annu. Rev. Chem. Biomol. Eng. 2010, 1, 149–173.
53. Antosova, Z.; Mackova, M.; Kral, V.; Macek, T. Therapeutic application of peptides and proteins: Parenteral forever? Trends Biotechnol. 2009, 27, 628–635.
54. Ward, B.P.; Ottaway, N.L.; Perez-Tilve, D.; Ma, D.; Gelfanov, V.M.; Tschop, M.H.; DiMarchi, R.D. Peptide lipidation stabilizes structure to enhance biological function. Mol. Metab. 2013, 2, 468–479.

55. Tugyi, R.; Uray, K.; Iván, D.; Fellinger, E.; Perkins, A.; Hubecz, F. Partial D-amino acid substitution: Improved enzymatic stability and preserved Ab recognition of a MUC2 epitope peptide. Proc. Natl. Acad. Sci. USA 2005, 102, 2021.

56. Rink, R.; Arkema-Meter, A.; Baudoin, I.; Post, E.; Kuipers, A.; Nelemans, S.A.; Akanbi, H.J.; Moll, G.N. To protect peptide pharmaceuticals against peptidases. J. Pharmacol. Toxicol. Methods 2010, 61, 210–218.

57. Sharman, A.; Low, J. Vasopressin and its role in critical care. Contin. Educ. Anaesth. Crit. Care 2008, 134–137.

58. Agersø, H.; Larsen, L.S.; Riis, A.; Lövgren, U.; Karlsson, M.O.; Senderovitz, T. Pharmacokinetics and renal excretion of desmopressin after intravenous administration to healthy subjects and renally impaired patients. Wiley Online Libr. 2004, 58, 352–358.

59. Harris, A.G. Somatostatin and somatostatin analogues: Pharmacokinetics and pharmacodynamic effects. Gut 1994, 35, S1–S4.

60. Kilian, G.; Jamie, H.; Brauns, S.C.A.; Dyason, K.; Milne, P.J. Biological activity of tyrosine-containing 2, 5-diketopiperazines. Die Pharm.-Int. J. Pharm. Sci. 2005, 60, 305–309.

61. Bycroft, B.; Payne, D. Dictionary of Antibiotics and Related Substances: With CD-ROM; CRC Press: Boca Raton, FL, USA, 2013.

62. Du, L.; Yang, X.; Zhu, T.; Wang, F.; Xiao, X.; Park, H.; Gu, Q. Diketopiperazine Alkaloids from a Deep Ocean Sediment Derived Fungus Penicillium sp. Chem. Pharm. Bull. 2009, 57, 873–876.

63. Michalský, J.; Čtvrtník, J.; Horáková, Z.; Bydžovský, V. Über die tuberkulostatische Aktivität von 2,5-Bis-(aminooxymethyl)-3,6-diketopiperazin, eines Umwandlungsproduktes des Cycloserins. Experientia 1962, 18, 217–218.

64. Miyazaki, K.; Yasutake, A.; Nishino, N.; Aoyagi, H.; Kato, T.; Izumiya, N. Cyclic peptides. X. Bitter taste and chymotryptic hydrolysis of cyclic depsidipeptides containing a tryptophan residue. Int. J. Pept. Protein Res. 1981, 17, 118–124.

65. Borthwick, A.D. 2,5-diketopiperazines: Synthesis, reactions, medicinal chemistry, and bioactive natural products. Chem. Rev. 2012, 112, 3641–3716.

66. Zhao, S.; Smith, K.S.; Deveau, A.M.; Dieckhaus, C.M.; Johnson, M.A.; Macdonald, T.L.; Cook, J.M. Biological activity of the tryprostatins and their diastereomers on human carcinoma cell lines. J. Med. Chem. 2002, 45, 1559–1562.

67. Prasad, C. Bioactive cyclic dipeptides. Peptides 1995, 16, 151–164.

68. Shiosaki, K. Toward development of peptidomimetics: Diketopiperazine templates for the Trp-Met segment of CCK-4. Pept. Chem. Struct. Biol. 1990, 978–980.

69. Deigin, V.; Ksenofontova, O.; Yatskin, O.; Goryacheva, A.; Ignatova, A.; Feofanov, A.; Ivanov, V. Novel platform for the preparation of synthetic orally active peptidomimetics with hemoregulating activity. II. Hemosuppressor activity of 2, 5-diketopiperazine-based. Int. Immunopharmacol. 2020, 81, 106185.
70. Deigin, V.; Ksenofontova, O.; Khrushchev, A.; Yatskin, O.; Goryacheva, A.; Ivanov, V. Chemical Platform for the Preparation of Synthetic Orally Active Peptidomimetics with Hemoregulating Activity. ChemMedChem 2016, 11, 1974–1977.