Available online on 15.04.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Emerging trends in therapeutic peptide pharmaceuticals: Prospects and perspectives

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ABSTRACT

Over the last few decades, the inclusions of peptide drugs in the pharmaceutical formulation aspects are more contemporary and recurrent. Since peptide moieties for the treatment of various clinical conditions has been started worthwhile since 1930's. There has been an increasingly sustainable research work regarding the formulation of therapeutic peptides are in the arena, as probably several entities are already in the clinical investigation, whereas few more are in the pipeline for clinical indication. In this current discussion, it has been aimed to unleash the potential of therapeutic bioactive peptides and its future prospects, in the area of pharmaceutical formulation. A plinth of area in regard to the, demand for the development of pharmaceutical formulation of bioactive peptides are still need to be uncovered. And hence only we have discussed deeply about the contemporary prospects of the peptide moieties.

Keywords: Peptide drugs, pharmaceutical formulation, current trends, clinical implications.

Article Info: Received 19 Feb 2019; Review Completed 29 March 2019; Accepted 05 April 2019; Available online 15 April 2019

Cite this article as:

Sangeetha N, Selvamani P, Latha S, Emerging trends in therapeutic peptide pharmaceuticals: Prospects and perspectives, Journal of Drug Delivery and Therapeutics. 2019; 9(2-s):606-610 **http://dx.doi.org/10.22270/jddt.v9i2-s.2622**

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INTRODUCTION

Numerous prospects of biopharmaceutical process development have been well examined over the past few decades. Complicatedness in fermentation, cell culture, and, to some extent, purification and recovery has largely been conquered and these process steps have been well characterized for the production of a lot of protein pharmaceuticals. Conversely, one important field lags behind these others in its development. The design and production of protein and peptide drug formulations is not well developed and many of the mechanisms for stabilization and delivery of these drugs are significant[1].

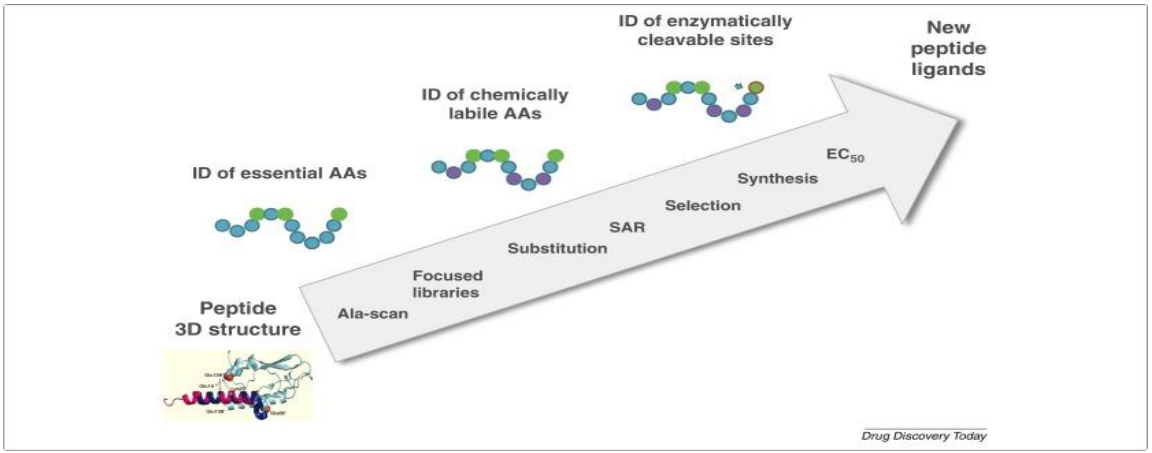

Figure 1: Current Scenario in peptide drug development

Peptides are recognized for being highly selective and efficacious and, at the same time, relatively safe and well tolerated. Consequently, there is an increased interest in peptides in pharmaceutical research and development (R&D), and approximately 140 peptide therapeutics are currently being evaluated in clinical trials. Given that the low-hanging fruits in the form of obvious peptide targets have already been picked, it has now become necessary to explore new routes beyond traditional peptide design. Examples of such approaches are multifunctional and cell penetrating peptides, as well as peptide drug conjugates[2-4]. Here, we discuss the current status, strengths, and weaknesses of peptides as medicines and the emerging new opportunities in peptide drug design and development as mentioned in Fig 1.

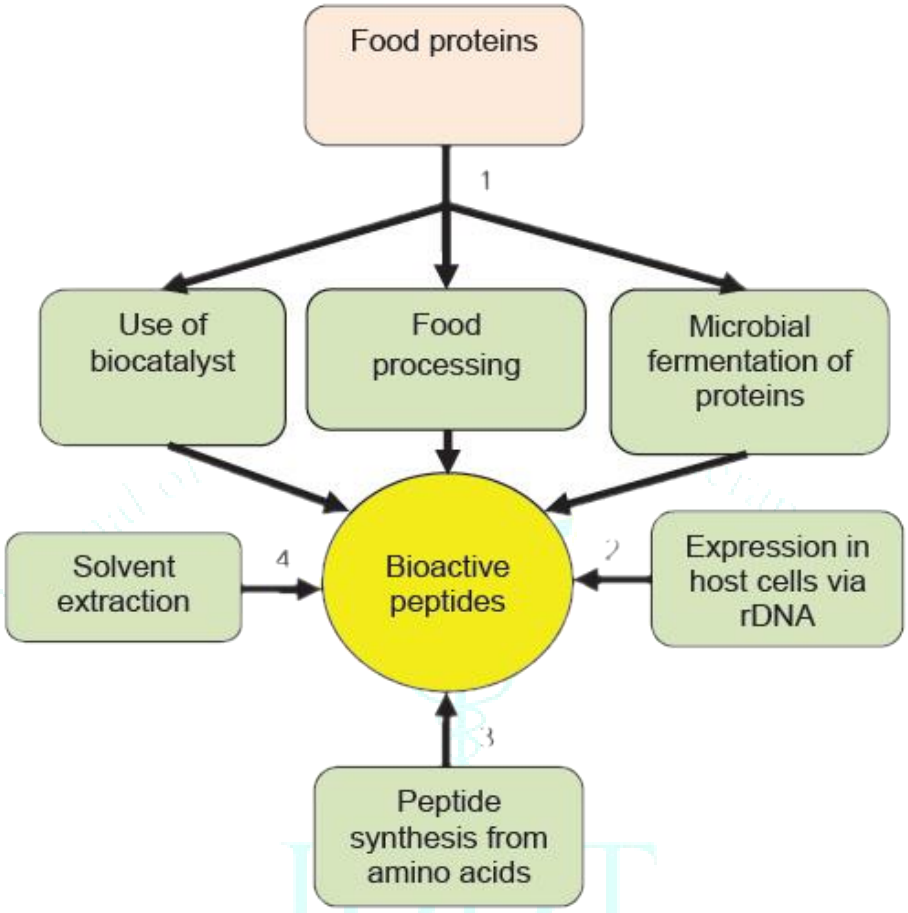

Figure 2: Pharmaceutical applications of Bioactive peptides

Proteins and peptides play important roles in living body systems by controlling, directing and/or coordinating inter- and intra-cellular communications and cellular function. From a nutritional perspective, peptides are more bioavailable than proteins or free amino acids. Further, peptides with low molecular weight have been known to be less allergenic than their native proteins, explaining why milk protein hydrolysates are widely utilized in the formulation of hypoallergenic infant foods. Additionally, as nature's tool kit; the diverse physiological roles of peptides make them suitable candidates for the development of therapeutic agents. There is a wide variety of physiological activities induced by bioactive peptides and these bioactivities are determined by the type, number, sequence and properties of amino acids present in the peptide. It is worth mentioning that whereas some proteins (such as lysozyme and α-lactalbumin) retain their bioactivities even the unhydrolysed denatured state, usually, the aforementioned bioactivities are latent until proteins are hydrolysed to release physiologically active peptides shown in Fig 2. Captured are some bioactive peptides and their bioactivities or areas of therapeutic applications. Bioactive peptides are therefore suitable candidates for a new era of pharmaceutical products, especially with the heightened concerns of side effects of small molecule drugs and the increased attention to fresher and 'greener' foods and nutraceuticals possessing health-preventing or health-promoting properties.

Marketed products and its clinical implications of Peptide drugs[5-8]

Brand Name	Common Name	Chemical Name	Intended purpose
Eraxis, Ecalta	Anidulafungin	1,2-dihydroxy-2-(4-hydroxyphenyl)ethyl]-11,20,21,25-tetrahydroxy-3,15-bis[(1R)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-1,4,7,13,16,22hexaazatricyclo [22.3.0.09,13]heptacosan-18-yl]-4-{4-[4-(pentyloxy) phenyl] phenyl}benzamide	Antifungal drugs that inhibits the synthesis of 1,3-β-D-glucan
Antocin	Atosiban acetate	c[Mpa-Tyr(Et)-Ile-Thr-Asn-Cys]-Pro-Orn-Gly-NH2,acetate [or [Mpa1, D-Tyr(Et)2, Thr4, Orn8]-oxytocin ,acetate]	Delaying the birth in case of threat of premature birth
Bacitracin, Cortisporin, Neosporin	Bacitracin	1-(N-((2-(1-amino-2-methylbutyl)-4,5-dihydro-4-thiazolyl)carbonyl)-L-leucine)	Infants with pneumonia and empyema caused by staphylococci
Angiomax	Bivalirudin	H-D-Phe-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr- Leu-OH, trifluoroacetate hydrate	Anticoagulant in patients with unstable angina undergoing PTCA or PCI
Velcade	Bortezomib	Pyz-Phe-boroLeu-(OH)2	Multiple myeloma, and refractory, mantle cell lymphoma
Bigonist	Buserelin	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-NHEt (or N-ethyl-prolinamide), acetate	Advanced prostate cancer
Miacalcin	Calcitonin	Cys-Gly-Asn-Leu-Ser-Thr-Cys-Met-Leu-Gly- Thr-Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-Thr-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro-NH2	Symptomatic Paget's disease for patients unresponsive to alternate treatments or intolerant to such treatments
Duratocin	Carbetocin acetate	c[Tyr(Me)-Ile-Gln-Asn-Cys((CH2)3CO2-)]-Pro-Leu-Gly-NH2, acetate	Prevention of uterine atony, induction,and control postpartum bleeding or haemorrhage
Cancidas	Caspofungin	5-((2-Aminoethyl)amino)-N(2)-(10,12-dimethyl tetradecanoyl)-4-hydroxy-L-ornithyl-L-threonyl-trans-4-hydroxy-L-prolyl--4-hydroxy-4-(P- hydroxyphenyl)-L-threonyl-threo-3-hydroxy-Lornithyl-trans-3-hydroxy-L-proline cyclic (6-1)-peptide	Antifungal drug
Capoten	Captopril	2-Methyl-3sulfanylpropanoyl]pyrrolidine-2-carboxylic acid	Renovascular hypertension
Cetrotide	Cetrorelix acetate	Ac-D-2Nal-D-4-chloroPhe-D-3-(3´ - pyridyl)Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH2, acetate	Inhibition of premature LH surges in women undergoing controlled ovarian stimulation
Colomycin, Coly-Mycin, Promixin.	Colistin	6,9,18-tris(2-aminoethyl)-3-[(1R)-1-hydroxyethyl]-12,15-bis(2-methylpropyl)-2,5,8,11,14,17,20-heptaoxo-1,4,7,10,13,16,19-heptaazacyclotricosan-21-yl]carbamoyl}propyl]carbamoyl}-2-hydroxypropyl] carbamoyl}propyl]-5-methylheptanamide	Acute or chronic infections due to sensitive strains of certain gram negative bacilli,
Gengraf, Neoral, Pulminiq, Restasis, Sandimmune	Cyclosporine	Cyclic(L-alanyl-D-alanyl-N-methyl-L-leucyl-Nmethyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl- L-2-amino-6-octenoyl-L-alphaamino-butyryl-N-methylglycyl-N-methyl-Lleucyl-L-valyl-N-met hyl-L-leucyl)	Transplant (kidney, liver, and heart) rejection, rheumatoid arthritis, severe psoriasis.
Cosmegen	Dactinomycin	2-amino-N,N'-bis(hexadecahydro-2,5,9-trimethyl-6,13-bis(1-methylethyl)-1,4,7,11,14-pentaoxo-1H-pyrrolo(2,1-l)(1,4,7,10,13)oxatetra-azacyclohexadecin-10-yl)-4,6-dimethyl-3-oxo-3H-phenoxazine-1,9-dicarboxamide.	Wilms'tumor, childhood rhabdomyosarcoma, Ewing's sarcoma and metastatic
Firmagon	Degarelix acetate	Ac-D-2Nal-D-4-chloroPhe-D-3-(3´ -pyridyl)Ala-Ser-4-aminoPhe(L-hydroorotyl)-D-4-aminoPhe(carbamoyl)-Leu-isopropylLys-Pro-D-Ala-NH2, acetate	Advanced prostate cancer
Cubicin	Daptomycin	*N*-Decanoyl-L-tryptophyl-L-asparaginyl-Laspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-Lalanine[egr]1-lactone	Complicated skin and skin structure infections caused by susceptible strains of Gram-positive microorganisms.
Fuzeon	Enfuvirtide	Ac-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH2	AIDS/HIV-1 infection
Vasotec	Enalapril maleate	(S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-Ala]-Pro-OH, maleate or (Z)-2-butenedioate	Hypertension
Integrilin	Eptifibatide	c[Mpa-homoArg-Gly-Asp-Trp-Pro-Cys]-NH2	Acute coronary syndrome,

			unstable angina undergoing PCI
Byetta	Exenatide	H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2 [Incretinmimetics (GLP-1 et GIP)]	Glycemic control in patients with type 2 diabetes mellitus
Agifutol	Glutathione	H-g-Glu-Cys-Gly-OH	Hepatic insufficiency, wound healing, inflammation of respiratory tract, asthenia
Zoladex	Goserelin	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-AzGly-NH2, acetate [or [DSer(OtBu)6,AzGly10]GnRH, acetate]	Advanced prostate cancer, breast cancer
Cibacalcin	Human calcitonin	H-c[Cys-Gly-Asn-Leu-Ser-Thr-Cys]-Met-Leu-Gly-Thr-Tyr-Thr-Gln-Asp-Phe-Asn-Lys-Phe-His-Thr-Phe-Pro-Gln-Thr-Ala-Ile-Gly-Val-Gly-Ala-Pro-NH2	Postmenopausal osteoporosis, Paget's disease, hypercalcaemia
Firazyr	Icatibant acetate	H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH, acetate	Hereditary angioedema
Somatuline Depot	Ianreotide acetate	H-2Nal-c[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2,acetate	Acromegaly, carcinoid syndrome
Refludan	Lepirudin or r-hirudin	H-Leu-Thr-Tyr-Thr-Asp-Cys-Thr-Glu-Ser-Gly-Gln-Asn-Leu-Cys-Leu-Cys-Glu-Gly-Ser-Asn-Val-Cys-Gly-Gln-Gly-Asn-Lys-Cys-Ile-Leu-Gly-Ser-Asp-Gly-Glu-Lys-Asn-Gln-Cys-Val-Thr-Gly-Glu-Gly-Thr-Pro-Lys-Pro-Gln-Ser-His-Asn-Asp-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln-OH	For the treatment of heparin-induced thrombocytopenia
Liraglutide	Victoza	H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-N6-[N-(1-oxohexadecyl)-L-g-Glu]-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-OH [GLP-1analogue]	Type 2 diabetes
Zestril, Prinivil	Lisinopril	(S)-1-[N2-(1-carboxy-3-phenylpropyl)-Lys]-Pro-OH	Hypertension,congestive heart failure
Diapid	Lypressin	H-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH2 [or 8-L-lysinevasopressine]	Central diabetes insipidus, Cushing's syndrome
Synarel	Nafarelin acetate	Pyr-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH2, acetate	Central precocious puberty, endometriosis, uterine fibroids, ovarian stimulation in in vitro fecundation
Natrecor	Nesiritide	Ser-Pro-Lys-Met-Val-Gln-Gly-Ser-Gly-[Cys-Phe-Gly-Arg-Lys-Met-Asp-Arg-Ile-Ser-Ser-Ser-Ser-Gly-leu-Gly-Cys]- Lys-Val-Leu-Arg-Arg-His-OH	Acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.
Sandostatin	Octreotide	H-D-Phe-c[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thol,acetate	Acromegaly, carcinoid syndrome
Syntocinon	Oxytocin	H-c[Cys-Tyr-Ile-Gln-Asn-Cys]-Pro-Leu-Gly-NH2	Initiation or improvement of uterine contractions, and control postpartum bleeding or haemorrhage
Fortical	Salmon calcitonin	H-c[Cys-Ser-Asn-Leu-Ser-Thr-Cys]-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH2	Postmenopausalosteoporosis, Paget'sdisease, hypercalcaemia
Saralasin acetate	Sarenin	H-Sar-Arg-Val-Tyr-Val-His-Pro-Ala-OH, acetate[1-Sarcosyl-8-Alanyl-angiotensin II]	Hypertension
Stilamin	Somatostatin acetate	H-Ala-Gly-c[Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr- Phe-Thr-Ser-Cys]-OH, acetate	Acute variceal bleeding
Rhinaaxia	Spaglumat magnesium	Ac-Asp-Glu-OH, magnesium or sodium salt	Allergic rhinitis and conjunctivitis
Zadaxin	Thymalfasin	Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glulle-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH	Chronic hepatitis B, chronic hepatitis C
Aggrastat	Tirofiban	2-(butylsulfonylamino)-3-[4-(4-piperidin-4-ylbutoxy)phenyl]propanoic acid	Acute coronary syndrome
Octastatin, Sanvar	Vapreotide acetate	H-D-Phe-c[Cys-Tyr-D-Trp-Lys-Val-Cys]-Trp-NH2, acetate	Esophageal Variceal Bleeding

Peptide is low and/or high molecular weight biopolymers, which acquiesce two or more amino acid on hydrolysis. Peptides are the standard constituent of the protoplasm of cells and are high molecular weight compounds comprising of alpha amino acid adjoined together by peptide linkages. These proteins serve as enzymes, structural element, hormones or immunoglobulin and are concerned in metabolic process, cell augmentation, immunogenic defense mechanisms and other genetic activities[9].

Peptides proteins are an significant class of biological material which are not only the necessary nutrients of human body, but some of the polypeptide hormones like insulin are used in treating an assortment of diseases consequential from hormonal deficiency. As this use of peptides for systemic handling of certain diseases is well accepted in medical practice, research activities are being directed towards the production of huge quantities by rDNA expertise.

Mainly common route of administration for protein drug delivery has been parenteral, although many other routes have been tried with varying degree of accomplishment. Routes likely, intraocular, rectal, vaginal pulmonary and intranasal mode will bring the drug to the systemic circulation while avoiding transit through the digestive system. A major factor that restricts the usefulness of these substances for their intended therapeutic function is that they are simply metabolized by plasma proteases when they arrive at the peripheral circulation. Besides, adverse effects connected with are relevant these drugs to the pulmonary or the other mucosal surfaces may be preventive[10-12].

Delivering therapeutically active protein by the oral route has been confronted and a goal for many years. For such drugs to be absorbed during the gastrointestinal tract, they must be protected from enzyme and must cross during the luminal barriers into the blood stream in an unchanged shape.

CONCLUSION

In this context, there has been a substantial potential for the development of peptide drugs, there has been an everlasting demand for various ailments and illness. However, to unleash the clinical implications of peptide drugs are in great need in recent times. And so only in this review the various aspects of peptide drugs currently in the market and those approved by the international authorities are also been discussed.

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