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FOOD AND DRUG ADMINISTRATION (FDA) APPROVED PEPTIDE DRUGS

Komalpreet Kaur*[1], Iqbal Singh, Pawandeep Kaur, Ramninder Kaur

[1*]Department of Pharmaceutical Chemistry, G.H.G. Khalsa College of Pharmacy, Gurusar Sadhar, Ludhiana, Punjab, India.

ABSTRACT

The decreasing number of approved drugs produced by the pharmaceutical industry, which has been accompanied by increasing expenses for R and D, demands alternative approaches to increase pharmaceutical R and D productivity. This situation has contributed to a revival of interest in peptides as potential drug candidates. New synthetic strategies for limiting metabolism and alternative routes of administration have emerged in recent years and resulted in a large number of peptide-based drugs that are now being marketed. This review reports on the unexpected and considers able number of peptides that are currently available as drugs and the chemical strategies that were used to bring them into the market. As demonstrated here, peptide-based drug discovery could be a serious option for addressing new therapeutic challenges.

KEYWORDS

Market prepared peptides as drug, Their activities, Mechanism of action and Their amino acids sequence.

Author for Correspondence:

Komalpreet Kaur,
Department of Pharmaceutical Chemistry,
G.H.G. Khalsa College of Pharmacy,
Gurusar Sadhar,
Ludhiana, Punjab, India.

Email: komalmpharm@gmail.com

INTRODUCTON

Peptides are generally considered to be poor drug candidates because of their low oral bioavailability and propensity to be rapidly metabolized. The concept that a drug can be not orally available has become more and more accepted and as a consequence, some pharmaceutical companies have contributed in recent years to a revival of interest in peptides as potential drug candidates[1]. New synthetic strategies to improve productivity and reduce metabolism of peptides, along with alternative routes of administration, have been developed in recent years, and a large number of peptide-based drugs are now being marketed.

Therapeutic peptides traditionally have been derived from three sources

Natural or bioactive peptides produced by plants, animal or human (derived from naturally occurring peptide hormones or from fragments of larger proteins)
Peptides isolated from genetic or recombinant libraries
Peptides discovered from chemical libraries[2].

Generally, the size of the peptide determines the most suitable technology for its production chemical synthesis, recombinant DNA technology, cell-free expression systems, transgenic animals and plants or enzymatic synthesis. With the use of unnatural amino acids and pseudo-peptide bonds, chemical synthesis offers access to a much wider chemical diversity than peptide derivatives produced by recombinant technologies, with a diversified potential for intellectual property (in terms of patentable new chemical entities). Large-scale chemical synthesis has become a viable technology for the production of small- and medium-sized peptides ranging from approximately 5 to 50 residues, and the chemical way is now often a better technological option than the biotechnological methods of recombinant DNA or bio catalysis for the synthesis of medium-sized peptides that comprise most of the pharmaceutically relevant molecules. In particular, production of synthetic therapeutic peptides has become possible for the pharmaceutical industry with recent developments of solid-phase peptide synthesis (SPPS).

Advantages of peptides over other drug candidates

Compared with proteins and antibodies, peptides have the potential to penetrate further into tissues owing to their smaller size. Moreover, therapeutic peptides, even synthetic ones, are generally less immunogenic than recombinant proteins and antibodies[3].

Peptides have other advantages over proteins and antibodies as drug candidates, including lower manufacturing costs (synthetic versus recombinant production), higher activity per unit mass (15-60-fold, assuming 75kD a for one combining site of an antibody and 10-50 amino acids for a therapeutic peptide), lower royalty stack than antibodies because of a simpler intellectual property landscape during discovery and manufacturing, greater stability (lengthy storage at room temperature acceptable) reduced potential for interaction with the immune system (assuming the peptide contains no known immune-system signaling sequence) and better organ or tumour penetration[4].

Therapeutic peptides also offer several advantages over small organic molecules that make up traditional medicines.

The first advantage is that often representing the smallest functional part of a protein, they offer greater efficacy, selectivity and specificity (limited non-specific binding to molecular structures other than the desired target) than small organic molecules.

A second advantage is that the degradation products of peptides are amino acids, thus minimizing the risks of systemic toxicity (minimization of drug interactions).

Third, because of their short half-life, few peptides accumulate in tissues (reduction of risks of complications caused by their metabolites). Most therapeutic peptides, which are mainly derived from natural peptides, are receptor agonists. Generally, small quantities of these peptide agonists are necessary to activate the targeted receptors. Few peptide antagonists, inhibiting lig and receptor interactions, have reached the market so far. As a general rule, antagonists must occupy more than 50% of the receptor population to be effective, in contrast to agonists, which require lower levels of receptor occupancy to be effective (normally between 5% and 20%)[5].

Market for synthetic therapeutic peptides

The market for synthetic therapeutic peptides rose from s5.3 billion in 2003 to s8 billion in 2005. It has been estimated that it will reach s11.5 billion in 2013. This excludes peptides, proteins and antibodies extracted from natural sources or produced by recombinant DNA technology, cell-free expression systems, transgenic animals and plants and enzyme technology. As described in Table No.1 more than 60 synthetic therapeutic peptides (comprising those used for medical diagnostics or imaging), with a size <50 amino acids, have reached the American, European and/or Japanese pharmaceutical markets through a marketing authorization as APIs, even if some of them are generics or discontinued[6].

Peptides and their homologous compounds (proteins and antibodies) can be used in multiple pathologies, including allergy and asthma, arthritis, baldness, cardiovascular diseases (coronary syndrome and angina) diabetes, gastrointestinal dysfunction growth problem, haemostasis, immunity disease, impotence, incontinence, infective diseases (bacterial, fungal and viral), inflammation, obesity, oncology (cancer and tumour imaging) osteoporosis (calcium metabolism dysfunction) pain, vaccines and so on, which represent important markets. In this context, the CNS is certainly a paradox: it is a major therapeutic area with unmet medical needs, for which the therapeutic peptide market potential is immense[7].

Table No.1: Synthetic therapeutic peptides that have reached American, European and/or Japanese pharmaceutical markets

INNs	Brand- names	Sequence	Indications
Anidulafungin	Eraxis, Ecalta	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-1,4,7,13,16,22-hexaazatricyclo[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
Atosiban acetate	Antocin	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	Bacitracin, Cortisporin, Neosporin	1-(N-((2-(1-amino-2-methylbutyl)-4,5-dihydro-4-thiazolyl)carbonyl)-L-leucine)	Infants with pneumonia and empyema caused by staphylococci
Bivalirudin	Angiomax	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
Bortezomib	Velcade	Pyz-Phe-boroLeu-(OH)2	Multiple myeloma, and refractory, mantle cell lymphoma
Buserelin	Bigonist	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-NHEt (or N-ethyl-prolinamide), acetate	Advanced prostate cancer
Calcitonin	Miacalcin	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
Carbetocin acetate	Duratocin	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
Caspofungin	Cancidas	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-L-ornithyl-trans-3-hydroxy-L-proline cyclic (6-1)-peptide	Esophageal candidiasis and invasive aspergillosis Not Available
Captopril	Capoten	2-Methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid	Renovascular hypertension
Cetrorelix acetate	Cetrotide	Ac-D-2Nal-D-4-chloroPhe-D-3-(3´ -	Inhibition of premature LH surges in

		pyridyl)Ala-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH2, acetate	women undergoing controlled ovarian stimulation
Colistin	Colomycin, Coly-Mycin, Promixin.	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,
Cyclosporine	Gengraf, Neoral, Pulminiq, Restasis, Sandimmune	Cyclic(L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-alpha-amino-butyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-met hyl-L-leucyl)	Transplant (kidney, liver, and heart) rejection, rheumatoid arthritis, severe psoriasis.
Dactinomycin	Cosmegen	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-I)(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
Degarelix acetate	Firmagon	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
Daptomycin	Cubicin	*N*-Decanoyl-L-tryptophyl-L-asparaginyl-L-aspartyl-L-threonylglycyl-L-ornithyl-L-aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-*threo*-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine[egr]$_1$-lactone	Complicated skin and skin structure infections caused by susceptible strains of Gram-positive microorganisms.
Enfuvirtide	Fuzeon	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
Enalapril maleate	Vasotec	(S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-Ala]-Pro-OH, maleate or (Z)-2-butenedioate	Hypertension
Eptifibatide	Integrilin	c[Mpa-homoArg-Gly-Asp-Trp-Pro-Cys]-NH2	Acute coronary syndrome, unstable angina undergoing PCI
Exenatide	Byetta	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
Glutathione	Agifutol	H-g-Glu-Cys-Gly-OH	Hepatic insufficiency, wound healing, inflammation of respiratory tract, asthenia
Goserelin	Zoladex	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-AzGly-NH2, acetate [or [D-Ser(OtBu)6,AzGly10]GnRH, acetate]	Advanced prostate cancer, breast cancer

Human calcitonin	Cibacalcin	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
Icatibant acetate	Firazyr	H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH, acetate	Hereditary angioedema
Ianreotide acetate	Somatuline Depot	H-2Nal-c[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2,acetate	Acromegaly, carcinoid syndrome
Lepirudin or r-hirudin	Refludan	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-1 analogue]	Type 2 diabetes
Lisinopril	Zestril, Prinivil	(S)-1-[N2-(1-carboxy-3-phenylpropyl)-Lys]-Pro-OH	Hypertension, congestive heart failure
Lypressin	Diapid	H-c[Cys-Tyr-Phe-Gln-Asn-Cys]-Pro-Lys-Gly-NH2 [or 8-L-lysinevasopressine]	Central diabetes insipidus, Cushing's syndrome
Nafarelin acetate	Synarel	Pyr-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH2, acetate	Central precocious puberty, endometriosis, uterine fibroids, ovarian stimulation in in vitro fecundation
Nesiritide	Natrecor	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.
Octreotide	Sandostatin	H-D-Phe-c[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thol,acetate	Acromegaly, carcinoid syndrome
Oxytocin	Syntocinon	H-c[Cys-Tyr-Ile-Gln-Asn-Cys]-Pro-Leu-Gly-NH2	Initiation or improvement of uterine contractions, and control postpartum bleeding or haemorrhage
Salmon calcitonin	Fortical	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
Somatostatin acetate	Stilamin	H-Ala-Gly-c[Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr- Phe-Thr-Ser-Cys]-OH, acetate	Acute variceal bleeding

Spaglumat magnesium	Rhinaaxia	Ac-Asp-Glu-OH, magnesium or sodium salt	Allergic rhinitis and conjunctivitis
Thymalfasin	Zadaxin	Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-lle- Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn-OH	Chronic hepatitis B, chronic hepatitis C
Tirofiban	Aggrastat	2-(butylsulfonylamino)-3-[4-(4-piperidin-4-ylbutoxy)phenyl]propanoic acid	Acute coronary syndrome
Vancomycin	Vancocin	22-(2-amino-2-Oxoethyl)-48-[2-O-(3-amino-2,3,6-trideoxy-3-methyl-alpha-L-lyxo-hexopyranosyl)-beta-D-glucopyranosyloxy]-5,15-dichloro-2,18,32,35,37-pentahydroxy-19-[(N-methyl-D-leucyl)amino]-20,23,26,42,44-pentaoxo-7,13-dioxa-21,24,27,41,43-pentaazaoctacyclo-3,5,8(48),9,11,14,16,29(45),30,32,34,36,38,46,49-pentadecaene-40-carboxylic acid	Serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) staphylococci.
Vapreotide acetate	Octastatin, Sanvar	H-D-Phe-c[Cys-Tyr-D-Trp-Lys-Val-Cys]-Trp-NH2, acetate	BOV
Ziconotide	Prialt	[Cys1-Cys16, Cys8-Cys20, Cys15-Cys25]-tricycloH-[Cys1-Lys-Gly-Lys-Gly-Ala-Lys-Cys8-Ser-Arg-Leu-Met-Tyr-Asp-Cys15-Cys16-Thr-Gly-Ser-Cys20-Arg-Ser-Gly-Lys-Cys25]-NH2,acetate	Severe chronic pain

Peptides as drugs

A revival of interest

Anidulafungin (Eraxis; Pfizer) is the newest echinocandin antifungal to be approved by the US Food and Drug Administration for the treatment of esophageal candidiasis, candidemia, and deep-tissue candidiasis. Anidulafungin is a semisynthetic lipopeptide synthesized from fermentation products of *Aspergillus nidulans*. The compound is a noncompetitive inhibitor of β-1,3-D-glucan synthase, which results in the selective inhibition of the synthesis of glucan, a major structural component of the cell wall of many pathogenic fungi that is not present in mammalian cells. A difference in glucan content determines the excellent activity of anidulafungin in fungi and the paucity of adverse effects in humans[8].

Atosiban (trade names Tractocile, Antocin, atosiban SUN) is an inhibitor of the hormones oxytocin and vasopressin. It is used as an intravenous medication as a labour represent (tocolytic) to halt premature labor. Although initial studies suggested it could be used as a nasal spray and hence would not require hospital admission, it is not used in that form. It was developed by Ferring Pharmaceuticals in Sweden and first reported in the literature in 1985. Originally marketed by Ferring Pharmaceuticals, it is licensed in proprietary and generic forms for the delay of imminent pre-term birth in pregnant adult women. Atosiban is a nonapeptide, desamino-oxytocin analogue, and a competitive vasopressin/oxytocin receptor antagonist (VOTra). Atosiban inhibits the oxytocin-mediated release of inositol trisphosphate from the myometrial cell membrane. As a result, there is reduced release of intracellular, stored calcium from the sarcoplasmic reticulum of myometrial cells, and reduced influx of Ca^{2+} from the extracellular space through voltage gated channels. In addition, atosiban suppresses oxytocin-mediated release of PGE and PGF from the decidua[9].

Bacitracin is a mixture of related cyclic peptides produced by organisms of the lichen form is group of *Bacillus subtilisvar* Tracy, first isolated in 1945. These

peptides disrupt both gram positive and gram negative bacteria by interfering with cell wall and peptidoglycan synthesis. Bacitracin is used as a topical preparation only (as it is highly toxic if used internally). In terms of adverse reactions only, in comparison with bacitracin, petroleum jelly possesses an equally low infection rate and minimal risk for induction of allergy. The widespread use of bacitracin, even for minor wounds where it is not useful, contributes to antibiotic resistance. Bacitracin interferes with the dephosphorylation of the 55-carbon, biphosphate lipid transport molecule C55-isoprenyl pyrophosphate (undecaprenyl pyrophosphate), which carries the building blocks of the peptidoglycan bacterial cell wall outside the inner membrane for construction. Bacitracin binds divalent transition metal ions (Mn(II), Co(II), Ni(II), Cu(II), and Zn(II)) which binds and oxidatively cleave DNA[10].

Bivalirudin (Angiomax or Angiox, manufactured by The Medicines Company) is a specific and reversible direct thrombin inhibitor (DTI). Chemically, it is a synthetic congener of the naturally occurring drug hirudin (found in the saliva of the medicinal leech *Hirudomedicinalis*).

Bivalirudin is a DTI that overcomes many limitations seen with indirect thrombin inhibitors, such as heparin. Bivalirudin is a short, synthetic peptide that is potent, highly specific, and a reversible inhibitor of thrombin. It inhibits both circulating and clot-bound thrombin, while also inhibiting thrombin-mediated platelet activation and aggregation. Bivalirudin directly inhibits thrombin by specifically binding both to the catalytic site and to the anion-binding exosite of circulating and clot-bound thrombin. Thrombin is a serine proteinase that plays a central role in the thrombotic process. It cleaves fibrinogen into fibrin monomers, activates Factor V, VIII, and XIII, allowing fibrin to develop a covalently cross-linked framework that stabilizes the thrombus. Thrombin also promotes further thrombin generation, and activates platelets, stimulating aggregation and granule release. The binding of bivalirudin to thrombin is reversible as thrombin slowly cleaves the bivalirudin-Arg_3-Pro_4 bond, resulting in recovery of thrombin active site functions[11].

Bortezomib (marketed as Velcade by Millennium Pharmaceuticals and Cytomib by Venus Remedies) is the first therapeutic proteasome inhibitor to be tested in humans. It is approved in the U.S. for treating relapsed multiple myeloma and mantle cell lymphoma. In multiple myeloma, complete clinical responses have been obtained in patients with otherwise refractory or rapidly advancing disease. The boron atom in bortezomib binds the catalytic site of the 26S proteasome with high affinity and specificity. In normal cells, the proteasome regulates protein expression and function by degradation of ubiquitylated proteins, and also cleanses the cell of abnormal or misfolded proteins. Clinical and preclinical data support a role in maintaining the immortal phenotype of myeloma cells, and cell-culture and xenograft data support a similar function in solid tumor cancers. While multiple mechanisms are likely to be involved, proteasome inhibition may prevent degradation of pro-apoptotic factors, permitting activation of programmed cell death in neoplastic cells dependent upon suppression of pro-apoptotic pathways. Recently, it was found that bortezomib caused a rapid and dramatic change in the levels of intracellular peptides that are produced by the proteasome. Some intracellular peptides have been shown to be biologically active, and so the effect of bortezomib on the levels of intracellular peptides may contribute to the biological and/or side effects of the drug[12].

Buserelin is a gonadotropin-releasing hormone agonist (GnRH agonist). The drug's effects are dependent on the frequency and time course of administration. GnRH is released in a pulsatile fashion in the postpubertal adult. Initial interaction of any GnRH agonist, such as buserelin, with the GnRH receptor induces release of FSH and LH by gonadotrophes. Long-term exposure to constant levels of buserelin, rather than endogenous pulses, leads to down regulation of the GnRH receptors and subsequent suppression of the pituitary release of LH and FSH. Like other GnRH agonists, buserelin may be used in the treatment of hormone-responsive cancers such as prostate cancer or breast cancer, estrogen-dependent conditions (such as endometriosis or uterine fibroids),

and in assisted reproduction. Buserelin is also marketed under the brand name Metrelef. Metrelef is approved to treat patients with endometriosis by suppression of ovarian hormone production. In ovulation induction Metrelef is used as a pituitary blockade as an adjunct to gonadotrophin administration.

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish. Miacalcin (calcitonin-salmon) injection, synthetic is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. Calcitonin-salmon is a calcitonin receptor agonist. Calcitonin-salmon acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Calcitonin-salmon appears to have actions essentially identical to calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action. The actions of calcitonin on bone and its role in normal human bone physiology are still not completely elucidated, although calcitonin receptors have been discovered in osteoclasts and osteoblasts[13].

Caspofungin (brand name Cancidas worldwide) is a lipopeptide antifungal drug from Merck and Co., Inc. discovered by James Balkovec, Regina Black and Frances A. Bouffard. It is a member of a new class of antifungals termed the echinocandins. It works by inhibiting the enzyme (1→3)-β-D-glucan synthase and thereby disturbing the integrity of the fungal cell wall. Caspofungin was the first inhibitor of fungal (1→3)-β-D-glucan synthesis to be approved by the United States Food and Drug Administration. Caspofungin is administered intravenously[14].

Cetrorelix acetate (trade name Cetrotide) is an injectable gonadotropin-releasing hormone (GnRH) an agonist. A syntheticdeca peptide, it is used to treat hormone-sensitive cancers of the prostate and breast (in pre-/perimenopausal women) and some benign gynaecological disorders (endometriosis, uterine fibroids and endometrial thinning). In addition, cetrorelix is used in assisted reproduction to inhibit premature luteinizing hormone surges. The drug works by blocking the action of GnRH upon the pituitary, thus rapidly suppressing the production and action of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). It is administered as either multiple 0.25 mg daily subcutaneous injections or as a single-dose 3 mg subcutaneous injection. The duration of the 3 mg single dose is four days if hCG is not administered within four days, a daily 0.25 mg dose is started and continued until hCG is administered[15].

Colistin (polymyxin E) is a polymyxin antibiotic produced by certain strains of *Paenibacillus polymyxa* var. *colistinus*. Colistin is a mixture of cyclic polypeptides colistin A and B. Colistin is effective against most Gram-negative bacilli and is used as a polypeptide antibiotic. It is commercially available as *'Colymonas'* (India marketed by Glenmark Pharmaceuticals ltd) and *'Koolistin'* (India, registered and marketed by Biocon ltd). Colistin is a decades-old drug that fell out of favor due to its nephrotoxicity. It remains one of the last-resort antibiotics for multi-drug-resistant *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter*. NDM-1metallo-β-lactamase multi drug-resistant Enter obacteriaceae have also shown susceptibility to Colistin. Colistin is a bactericidal drug that binds to lipopolysaccharides and phospholipids in the outer cell membrane of Gram-negative bacteria. It competitively displaces divalent cations from the phosphate groups of membrane lipids, which leads to disruption of the outer cell membrane, leakage of intracellular contents, and bacterial death. In addition to its bactericidal effect, colistin can bind and neutralize lipopolysaccharide (LPS) and prevent the pathophysiologic effects of endotoxin in the circulation[16].

Cyclosporine, the active principle in Sandimmune (cyclosporine) is a cyclic polypeptide immuno suppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Beauveria nivea*. The exact mechanism of action is unknown but seems to be related to the inhibition of production and release of interleukin-2, which is a proliferative factor necessary for the induction of cytotoxic T lymphocytes in response to all antigenic challenge, and which plays a major role in both cellular and humoral immune responses. Cyclosporine

does not affect the nonspecific defense system of the host and does not cause significant my elosuppression.

Dactinomycin is the most significant member of actinomycines, which are a class of polypeptide antitumor antibiotics isolated from soil bacteria of the genus *Streptomyces.* In cell biology, Actinomycin D is shown to have the ability to inhibit transcription. Actinomycin D does this by binding DNA at the transcription initiation complex and preventing elongation of RNA chain by RNA polymerase[17].

Degarelix or degarelix acetate (trade name Firmagon) is a hormonal therapy used in the treatment of prostate cancer. During development it was known as FE200486. Degarelix has an immediate onset of action, binding to gonadotropin-releasing hormone (GnRH) receptors in the pituitary gland and blocking their interaction with GnRH. This induces a fast and profound reduction in luteinising hormone (LH), follicle-stimulating hormone (FSH) and in turn, testoster one suppression[18].

Daptomycin is a lipopeptide antibiotic used in the treatment of systemic and life-threatening infections caused by Gram-positive organisms. It is a naturally occurring compound found in the soil saprotroph *Streptomyces roseosporus*. Its distinct mechanism of action makes it useful in treating infections caused by multiple drug-resistant bacteria. It is marketed in the United States under the trade name Cubicin by Cubist Pharmaceuticals. Daptomycin has a distinct mechanism of action, disrupting multiple aspects of bacterial cell membrane function. It inserts into the cell membrane in a phosphatidylglycerol-dependent fashion, where it then aggregates. The aggregation of daptomycin alters the curvature of the membrane, which creates holes that leak ions. This causes rapid depolarization, resulting in a loss of membrane potential leading to inhibition of protein, DNA, and RNA synthesis, which results in bacterial cell death[19].

Enfuvirtide is an HIVfusion inhibitor, the first of a novel class of antiretroviral drugs used in combination therapy for the treatment of HIV-1 infection. It is marketed under the trade name Fuzeon (Roche). Enfuvirtide works by disrupting the HIV-1 molecular machinery at the final stage of fusion with the target cell, preventing uninfected cells from becoming infected. A biomimetic peptide, enfuvirtide was designed to mimic components of the HIV-1 fusion machinery and displace them, preventing normal fusion. Drugs that disrupt fusion of virus and target cell are termed entry inhibitors or fusion inhibitors[30].

Eptifibatide (Integrilin, Millennium Pharmaceuticals, also co-promoted by Schering-Plough/ Essex) is an antiplatelet drug of the glycoprotein IIb/IIIa inhibitor class. Eptifibatide is a cyclichepta peptide derived from a protein found in the venom of the southeastern pygmy rattlesnake (*Sistrurus miliarius barbouri*). It belongs to the class of the arginin-glycin-aspartat-mimetics and reversibly binds to platelets. Eptifibatide has a short half-life. The drug is the third inhibitor of GPIIb/IIIa that has found broad acceptance after the specific antibody abciximab and the non-peptide tirofiban entered the global market[20].

Exenatide (marketed as Byetta, Bydureon) derived from a compound found in the saliva of the Gila monster, a large lizard native to the southwestern US, is a functional analog of Glucagon-Like Peptide-1 (GLP-1), a naturally occuring peptide. Exenatide is a functional analog of the human incretin Glucagon-Like Peptide-1 (GLP-1). Incretins enhance glucose-dependent insulin secretion and exhibit other anti-hyperglycemic actions following their release into the circulation from the gut. The GLP-1 system increases insulin secretion only in the presence of elevated plasma glucose levels, avoiding in appropriately high insulin levels during fasting. The drug also moderates peak serum glucagon levels during hyperglycemic periods following meals, but does not interfere with glucagon release in response to hypoglycemia. Secondary effects of drug administration reduce the rate of gastric emptying and decreases food intake, mitigating the potential severity of hyperglycemic events after meals[21].

Goserelin acetate (Zoladex, Astra Zeneca) is an injectable gonadotropin releasing hormo nesuperagonist (GnRH agonist), also known as a luteinizing hormone releasing hormone (LHRH) agonist. Structurally, it is a decapeptide. Goserelin acetate is used to suppress production of the sex hormones (testosterone and estrogen), particularly in the treatment of breast and prostate cancer. Goserelin

acetate stimulates the production of the sex hormones testosterone and estrogen in a non-pulsatile (non-physiological) manner. This causes the disruption of the endogenous hormonal feedback systems, resulting in the down-regulation of testosterone and estrogen production[31].

Human Calcitonin (Cibacalcin) is an hormonal agent indicated for patients with Paget's disease. The calcitonins are polypeptidehormones secreted by the thyroid human calcitonin is a synthetic product classified as an orphan drug. Calcitonin reduces the rate of bone turnover, possibly by an initial blocking of bone resorption, resulting in decreases in serum alkaline phosphatase (reflecting decreased bone formation) and decreases in urinary hydroxyproline excretion (reflecting decreased bone resorption, i.e., breakdown of collagen)[22].

Icatibant (trade name Firazyr, alternative name Hoe 140, JE 049) is a peptidomimetic drug consisting of ten amino acids, which is a selective and specific antagonist of bradykinin B2 receptors. It has been approved by the European Commission for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase-inhibitor deficiency. Mechanism of action Bradykinin is a peptide-based hormone that is formed locally in tissues, very often in response to a trauma. It increases vessel perme ability, dilates blood vessels and causes smooth muscle cells to contract. Bradykinin plays an important role as the mediator of pain. Surplus bradykinin is responsible for the typical symptoms of inflammation, such as swelling, redness, overheating and pain. These symptoms are mediated by activation of bradykinin B2 receptors. Icatibant acts as a bradykinin inhibitor by blocking the binding of native bradykinin to the bradykinin B2 receptor.

Lanreotide is a medication used in the management of acromegaly and symptoms caused by neuroendocrine tumors, most notably carcinoid syndrome. It is a long-acting analogue of somatostatin, like octreotide.Lanreotide (as lanreotide acetate) is manufactured by Ipsen, and marketed under the trade name Somatuline. It is available in several countries, including the United Kingdom, Australia and Canada, and was approved for sale in the United States by the Food and Drug Administration (FDA) on August 30, 2007[23].

Lepirudin is an anticoagulant that functions as a direct thrombin inhibitor. Brand name Refludan, Generic: Lepirudin rDNA for injection. Lepirudin is a recombinant hirudin derived from yeast cells. It is almost identical to hirudin extracted from *Hirudo medicinalis*. It differs by the substitution of leucine for isoleucine at the N-terminal end of the molecule and the absence of a sulfate group on the tyrosine at position 63. Lepirudin may be used as an anticoagulant when heparins (unfractionated or low-molecular-weight) are contraindicated because of heparin-induced thrombocytopenia.

Liraglutide is a long-acting glucagon-like peptide-1 receptor agonist, binding to the same receptors as does the endogenous metabolichormone GLP-1 that stimulates insulin secretion. Marketed under the brand name Victoza, it is an injectable drug developed by Novo Nordisk for the treatment of type 2 diabetes. In 2015 Novo Nordisk began marketing it in the US. Under the brand name Saxenda as a treatment for obesity in adults with at least one weight-related comorbid condition. The product was approved for treatment of type 2 diabetes by the European Medicines Agency (EMA) on July 3, 2009, and by the US. Food and Drug Administration (FDA) on January 25, 2010. More recently, Liraglutide was approved by the FDA on December 23, 2014 for treatment for obesity in adults with some related comorbidity.

Nafarelin is a gonadotropin-releasing hormone agonist (GnRH agonist). Its proposed mechanism of action is the desensitization of pituitary GnRH receptors leading to a decrease in gonadotropin release, and ovarian hormone serum concentrations similar to those achieved in postmenopausal women. It decreases pituitary secretion of the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH). Nafarelin may be used in the treatment of estrogen-dependent conditions (such as endometriosis or uterine fibroids) to treat central precocious puberty, or to control ovarian stimulation in IVF. Nafarelin acetate is marketed by Searle (now part of Pfizer) under the brand name Synarel. It is delivered via a nasal spray.

Octreotide (brand name Sandostatin, Novartis Pharmaceuticals) is an octapeptide that mimics natural somatostatin pharmacologically, though it is a more potent inhibitor of growth hormone, glucagon, and insulin than the natural hormone. It was first synthesized in 1979 by the chemist Wilfried Bauer. Octreotide binds to somatostatin receptors. These receptors are coupled via pertussis toxin sensitive G proteins which lead to inhibition of adenylyl cyclase. Octreotide binding to these receptors also stimulates phosphotyrosine phosphatase and activation of the Na(+)/H(+) exchanger via pertussis toxin insensitive G proteins.

Oxytocin (Oxt) is a nonapeptidehormone in mammals. It is also available as a medication. Oxytocin is normally produced in the hypothalamus and stored in the posterior pituitary gland. It plays a role in intimacy, sexual reproduction of both sexes, and during and after childbirth as well as social bonding. It is released in large amounts after distension of the cervix and uterus during labor and with stimulation of the nipples following child birth. This helps with birth, maternal bonding, and lactation. Oxytocin is destroyed in the gastrointestinal tract, so it must be administered by injection or as nasal spray. It has a half-life of typically about three minutes in the blood when given intravenously. When administered intranasally via a nasal spray, oxytocin crosses the blood-brain barrier and exhibits psychoactive effects in humans. Unlike the case of intravenous administration, intranasal oxytocin has duration of at least 2.25 hours and as long as 4 hours[24].

Saralasin is a partial agonist of angiotensin II receptors, though it is commonly mistaken as a competitive antagonist. Saralasin's distinction as a partial agonist is based on the fact that its therapeutic effect (i.e. reduced hypertension) is only observed in patients with high plasma angiotensin II levels, but in patients with low angiotensin II levels Saralasin causes hypertension. In other words, the effects of Saralasin on the angiotensin II receptor in the absence of angiotensin II is pharmacodynamically similar to angiotensin II itself thus it is a partial agonist, because if it was an antagonist it would not elicit an effect when bound to its receptor. Saralasin is an angiotensin II analogue, containing sarcosine-1 and alanine-8, hence the name (sarcosine, alanine, angiotensin)[25].

Somatostatin (also known as growth hormone-inhibiting hormone (GHIH) or somatotropin release-inhibiting factor (SRIF)) or somatotropin release-inhibiting hormone[*citation needed*] is a peptide hormone that regulates the endocrine system and affects neuro transmission and cell proliferation via interaction with G protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones. Somatostatin inhibits insulin and glucagon secretion. Somatostatin has two active forms produced by alternative cleavage of a single preproprotein one of 14 amino acids, the other of 28 amino acids which is the short form with another 14 amino acids at one end. Among the vertebrates, there exist six different somatostatin genes that have been named SS1, SS2, SS3, SS4, SS5, and SS6. Zebrafish have all 6. The six different genes along with the five different somatostatin receptor sallowsomatostatin topossess a large range of functions. Humans have only one somatostatin gene, SST[26].

Thymalfasin is a chemically synthesized version of thymosin alpha 1 that is identical to human thymosin alpha 1. Thymosin alpha 1 is an acetylated polypeptide. Thymosin alpha 1 is now approved in 35 developing countries for the treatment of Hepatitis B and C. It is also used to boost the immune response in the treatment of other diseases. The mechanism of action of thymalfasin is not completely understood but is thought to be related to its immune modulating activities, centered primarily around augmentation of T-cell function. In various in vitro assays, thymosin alpha 1 has been shown to promote T-cell differentiation and maturation for example, CD4+, CD8+, and CD3+ cells have all been shown to be increased. Thymosin alpha 1 has also been shown to increase production of IFN-g, IL-2, IL-3, and expression of IL-2 receptor following activation by mitogens or antigens, increase NK cell activity, increase production of migratory inhibitory factor (MIF), and increase antibody response to T-cell dependent antigens.

Tirofiban (trade name Aggrastat) is an antiplateletdrug. It belongs to a class of antiplatelet

named glycoprotein IIb/IIIa inhibitors. Tirofiban is the first drug candidate whose origins can be traced to a pharmacophore-based virtual screeninglead. Aggrastat is a reversible antagonist of fibrinogen binding to the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. When administered intravenously, Aggrastat inhibits ex vivo platelet aggregation in a dose- and concentration-dependent manner[27].

Vancomycin is antibacterial obtained from *Streptomycesorientalis*. It is a glycopeptide related to ristocetin that inhibits bacterial cell wall assembly and is toxic to kidneys and the inner ear. The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. Specifically, vancomycin prevents incorporation of N-acetylmuramic acid (NAM)- and N-acetylglucosamine (NAG) peptide subunits from being incorporated into the peptidoglycan matrix; which forms the major structural component of Gram-positive cell walls. The large hydrophilic molecule is able to form hydrogen bond interactions with the terminal D-alanyl-D-alanine moieties of the NAM/NAG-peptides. Normally this is a five-point interaction. This binding of vancomycin to the D-Ala-D-Ala prevents the incorporation of the NAM/NAG- peptide subunits into the peptidoglycan matrix. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics. Vancomycin is not active in vitro against gram-negative bacilli, mycobacteria, or fungi[28].

Ziconotide (Prialt) is an atypical analgesic agent for the amelioration of severe and chronic pain. Derived from *Conus magus* (Cone Snail), it is the synthetic form of an ω-conotoxinpeptide. Ziconotide is a hydrophilic molecule that is freely soluble in water and is practically insoluble in methyl t-butyl ether. Ziconotide acts as a selective N-type voltage-gated calcium channelblocker. This action inhibits the release of pro-nociceptive neurochemicals like glutamate, calcitonin gene-related peptide (CGRP), and substance P in the brain and spinal cord, resulting in pain relief[29].

CONCLUSION

Peptides have gained increased interest as therapeutics during recent years. More than 60 peptide drugs have reached the market for the benefit of patients and several hundreds of novel therapeutic peptides are in preclinical and clinical development. The key contributor to this success is the potent and specific, yet safe, mode of action of peptides. The future development of peptide drugs will continue to build upon the strengths of naturally occurring peptides, with the application of traditional rational design to improve their weaknesses, such as their chemical and physical properties. The emerging peptide technologies, including multifunctional peptides, cell penetrating peptides and peptide drug conjugates, will help broaden the applicability of peptides as therapeutics. Taking all of the above into account, which are convinced that peptides offer enormous growth potential as future therapeutics for the treatment of unmet medical needs.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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