Review Article

Open Access

International Journal on Toxicology and Novel Drug Delivery

ijtn@scientificeminence.com

Review on Peptides as Therapeutic: The Art of Transforming Peptides into Drugs

Harendra Bisht*

Department of Pharmaceutical Science, Kumaun University, Nanital (India)

*** Corresponding Author**

Harendra Bisht, Department of Pharmaceutical Science, Kumaun University, Nanital (India), Tel: 8171232896, E-mail: hsb.bisht40@gmail.com

Citation

Harendra Bisht (2021) Review on Peptides as Therapeutic: The Art of Transforming Peptides into Drugs. Int J Toxicol and Novel Drug Delivery 1(1):101

Publication Datess

Received date: August 29, 2021

Accepted date: September 29, 2021

Published date: September 30, 2021

Abstract

Peptides and peptidomimetics played an essential role in development of a number of drugs, diagnostic antibodies and so on. Peptides having a wide range of therapeutic area like antimicrobials, anti-cancers, anti-hyperlipidaemic, anti-oxidants, antivirals, anti-diabetics, Cardiovascular agents and many others. There is huge no of natural sources where the peptides are obtained including Plant, animal, mineral and Marine etc. over a period of last 4-5 decades more then 300 peptides are investigated and successfully converted into drug candidate and also marketed. Many of the biotechnological techniques are involved in productions of peptides in associated with peptide source. These bioactive peptides provide us a wide range of investigation areas for research and development of new drug entities. At the molecular or Genetic level peptides also shows significant effects on host cell. This review provides us comprehensive overview on potent application, sources and production of peptides.

Keywords: Bioactive Peptides; Antihypertensive; Anticancer; Immune Response; Peptidomimetics

Introduction

From the last four decades a remarkable number of therapeutic active peptides has been originated or discovered and characterized they includes neuropeptides, peptides as vasoactive, hormonal peptides, genetic peptides etc. [1]. As a consequence of resulting pharmacodynamics interaction with their specific receptors these biologically active peptides alter the call functions as well as control its physiological functions. Now a day's peptides are emerging field of biomedical research because having a vital range of therapeutic application in various abnormal heath conditions. [2]

Peptides are composed of two or more amino acid monomers linked together *via* peptide bonds. Peptides are naturally occurring biologically active molecule in human body. Depending on the no of amino acid subunit peptides are called dipeptides, tripeptides, tetrapeptides and so on. Peptides are present in the part of every cell or tissue in the body. Like Proteins are synthesized naturally from the transcription of a sequence of specific genetic code, DNA. DNA gene connected into messenger mRNA then a long chain of amino acid joined together by peptide bond formation from a single molecule of peptide. Peptides are very specific in activity when compared to small molecules when used as a drug molecule. [3]

Peptides play a series of vital or essential functions in human body. Regulation of appropriate concentration and activity levels of peptides is mandatory to achieve homeostasis and physical as well as mental health. The purpose of a peptide carries out is dependent on which type of amino acid sequence are present in proteins. As well as the structure or specific shape of peptides. Peptides primarily binds membrane bound receptors and gives respective biological effects. [4]

Peptides having fewer side effects, peptides have become popular candidates for drug design. Peptide therapeutics have played a notable role in medical practice since the advent of insulin therapy in the 1920s. Over 60 peptide drugs are approved in the United States and other major markets, and peptides continue to enter clinical development at a steady pace. Despite this, advances in large no of docking models are only on the merge of making their contribution to peptide drug development.

Historic overview of Bioactive Peptide Development

The origin of peptide was exemplified by isolation and first bioactive use of insulin in the 1920s in diabetics who did not produce sufficient quantities of the hormone. After that isolation of ACTH peptide from animal tissues which is applied for the treatment of various endocrine disorders. Then peptides are used in replacement therapies as well as supplement preparations. Here is a list peptides development overview. [5]

Over 70 peptide drugs have been approved in the United States, Europe, and Japan; over 160 are in active clinical development and an additional more than 300 have been tested in human clinical trials. Here we review the characteristics of peptide drugs and clinical candidates, therapeutic applications. [6]

Peptide Name	Source	Introduction yaar to the clinic
Insulin	Isolated from canine and bovine pancreata	1920s
Adrenocorticotropic hormone	Isolated from bovine and porcine pituitary glands	1950s
Oxytocin	Synthetic	1962
Vasopressin	Synthetic	1962
Calcitonin	Isolated from salmon ultimobranchial gland	1971
Octreotide	Synthetic analog of somatostatin	1988
Leuprorelin	Synthetic analog of gonadorelin	1984

List of Source or chemical nature of early discovered peptides

Name of Drug	Target Involved	Receptor mechanism
Losartan and other sartans	Angiotensin II receptor 1	Antagonism
Small-molecule opioids	Opioid receptors	Agonism
Tolvaptan	Vasopressin V2 receptor	Antagonism
Bosentan	Endothelin receptors	Antagonism
Aprepitant	Neurokinin 1 receptor	Antagonism
Elagolix	Gonadotrophin-releasing	
hormone receptors	Antagonism	

Examples of few drugs act on peptide molecules

Therapeutic approaches of Peptides

Peptide as Anticancer agent

Peptides are very useful to develop the anticancer agents. Now a day's various research is also going on peptides as drug candidate application in tumours. According to treatment strategies peptides are divided into three main categories: (a) Neoplasm targeting peptides, (b) Cell-permeable peptides and (c) antimicrobial peptides. [7]

Peptides as antidiabetic agents

The gut-derived peptide hormone glucagon-like peptide 1 (GLP-1) are useful in treatment of obesity and type 2 diabetes. However, GLP-1 analogues have modest weight lowering capacity, in the range of 6–12%, and the therapeutic window is hampered by dose-dependent side effects. last few years, a new concept has emerged: combining the beneficial effects of several key metabolic hormones into a single molecular entity. Several unimolecular GLP-1-based polyagonists have shown higher metabolic action compared to GLP-1 consisting monotherapies. [8]

5% of the world's adult population is obese, and about 500 million people suffer from diabetes disorder. These conditions are both corelated with significant morbidity, mortality rate. Therefore, discovery of new pharmacological treatments is an imperious. Relative hyperglucagonemia is seen in all types of diabetes, and has been involve in its pathogenesis. Consequently, clinical trials are undertaken using various drugs

Merits	Demerits
wide ranges of therapeutic targets	Oral bioavailability is low
Less side effects and ADRs	Poor Bioactivity
Minimum toxicity	Low solubility
High potency of activity	Rapid Clearance
Hight chemical and biological Diversity	Expensive manufacturing cost
Target selectivity and specificity	Poor membrane permeability
Less accumulation in tissue	Metabolic Instability.

Merits and Demerits of therapeutic peptides

There are list of peptides which is used as antineoplastic agents and their cellular targets:

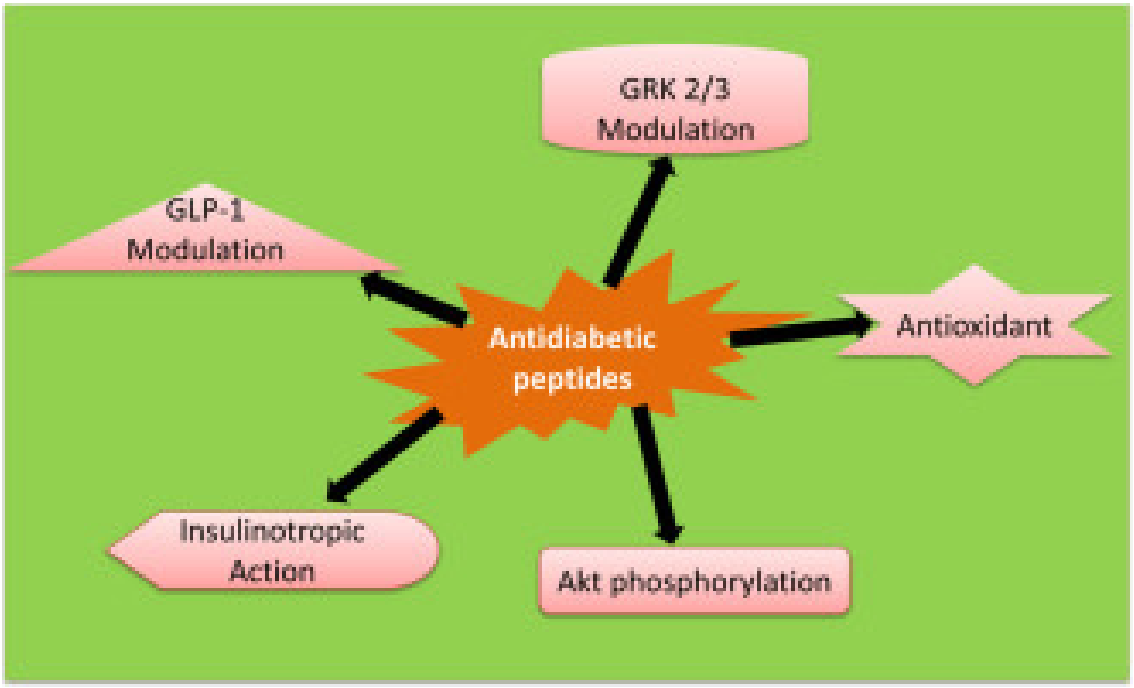
Name of Peptides	Examination method	Observation in cell culture
BR2	In-vitro	Colon cancer, cervical carcinoma, Murine Melanoma
Dox-TAT peptide	In-vitro	Brest cancer and rat prostate carcinoma cells
Magainin II	in vitro	Bladder cancer cells: RT4 pathologic grade 1
NRC-3 and NRC-7	In vitro & in vivo	Breast cancer: MDA-MB-468, SKBR3, MCF-7 and paclitaxel resistant MCF-7 (MCF-7-TX400) and murine mammary 4 T1 carcinoma cells
RGD-SSL-Dox	In vitro & in vivo	Melanoma (A375) and murine (B16-F10) melanoma cells
Buforin IIb	In vitro & in vivo	Cervical carcinoma (HeLa), leukaemia (Jurkat cells) and lung cancer
LPD-PEG-NGR	In vitro & in vivo	Fibrosarcoma (HT-1080) cells
PNC-2 and PNC-7	in vitro	Pancreatic cancer (MIA-PaCa) cells
p16	In vitro	Pancreatic cancer (AsPC-1 and BxPC-3) cells
Pen-ELP-p21	In vitro	Cervical carcinoma (HeLa) and ovarian carcinoma (SKOV-3) cells
Bac-7-ELP-p21	In vitro	Ovarian carcinoma
BACl-ELP-H1	In vivo	Glioma (U-87 MG and D54) and murine glioma (C6) cells
Pen-ELP-H1	In vitro	Breast cancer (MCF-7) cells
PNC-28	In vitro & in vivo	Breast cancer (MDA-MB-453), colon cancer (H1299 and SW1417), osteosarcoma (SAOS2), cervical carcinoma (HeLa)
PNC-27	In vitro	Rat k-ras-transformed pancreatic cancer (TUC-3) and transformed endothelial (E49) cells
CT20p-NP	In vitro & in vivo	Cervical carcinoma (HeLa) and murine mammary carcinoma (TS/A) cells
RRM-IL12	In vitro	Mouse melanoma (B16-F10) cells
Poropeptide-Bax	In vitro	Melanoma (SK-MEL-28) cells
RRM-MV	In vitro	malignant melanoma (MM96L), and murine melanoma (B16-F10) cells

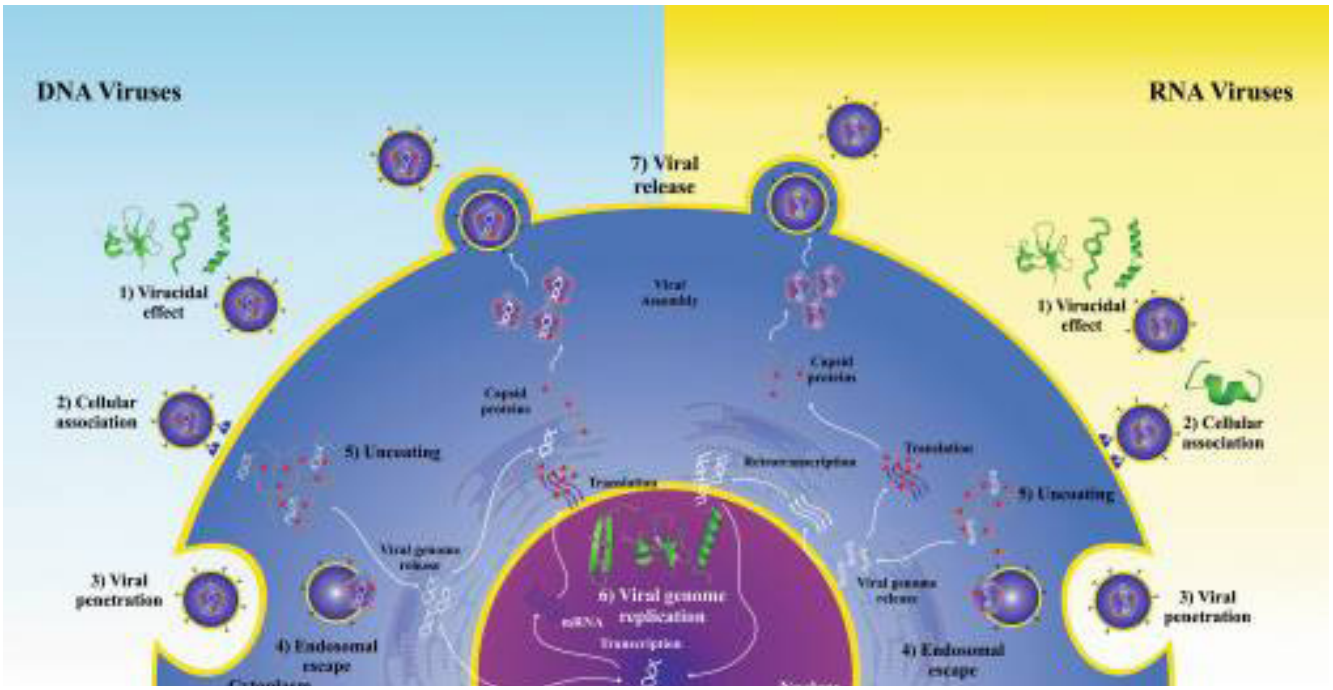
which inhibits glucagon activity to treat type 2 diabetes. As contrast, glucagon can increase energy expenditure. Therefore, researchers are planning peptides that combine sensitize of the glucagon receptor for further incretin properties, which will treat obesity while mitigating the hyperglycaemic effects of glucagon. [9,10]

Peptides as antiviral Agent

Peptides with antiviral activity are greatly increased over the period of worldwide influenza pandemic. [11]

Figure 02 Antiviral peptide inhibition sites on viral replication cycle. The antiviral peptides with a described mechanism of action were placed in their inhibition sites as follows: 1, virion inhibition; 2, adsorption; 3, viral penetration; 4, endosomal escape; 5, viral uncoating; 6, viral genome replication and 7, release of mature virions.





Peptide Name	Type of viral serotype	Genetic sequence	Genetic Conformation
P1 cyclic	H9N3	CNDFRSKTC	Cyclic
FluPep 1	H1N1	WLVFFVIAYFFR	Alpha-helix
FluPep 2	H1N1	WLVFFVIAYFAR	Alpha-helix
FluPep 3	H1N1	WLVFFVIFYFFRRRKKX	Alpha-helix
FluPep 4	H1N1	RRKKWLVFFVIFYFFR	Alpha-helix
FluPep 7	H1N1	RRKKIFYFFR	Alpha-helix
FluPep 8	H1N1	WLVFFVRRKK	Alpha-helix
Flufirvitide	Broad spectrum, H7N7	Various sequence	Various conformation
Defensins	H1N1, H3N2	ACYCRIPACIAGERRY	Beta-sheet
Killer peptide	H7N1	AKVTMTCSAS	Alpha-helix

Peptides as antihypertensive Agent

High blood pressure or hypertension is a condition that leads to various chronic disease in human being like Myocardial infraction, chronic kidney disease, congestive heart failure, haemorrhage stroke and so on. In food sources we have bioactive peptides are available which having antihypertensive properties, they have attracted attention of researcher and scientific community. Various operations like food derived peptides, enzyme hydrolysis, rDNA technology can use to produce biologically active peptides from food source such as dairy products cereals, legumes, milk derived and various fish species. [12,13]

Enzymatic hydrolysis by digestive enzymes

According to literature survey the common method of producing antihypertensive peptides from food proteins source is enzymatic hydrolysis. Many of the Angiotensin Converting Enzyme (ACE) inhibitory peptides have been produced using gastrointestinal enzymes, by the help of pepsin and trypsin. Enzymes obtained from plant (e.g., Papain) and animal sources (e.g., pepsin and trypsin), have also been used in producing bioactive antihypertensive peptides. [14]

Peptides produces by fermentation process

There are various industrially utilized dairy starter cultures which are highly proteolytic in nature and can be used for production of hypertension treating peptides by using fermentation process. A number of peptide products are synthesized and running in clinical trials for bioassay. The lactic acid bacteria (LAB) like Lactococcus lactis, Lactobacillus helveticus and L. delbrueckii ssp. Bulgaricus consists of a cell wall-bound proteinase and other intracellular peptidases, including endo peptidases, amino peptidases and dipeptidases. Many dietary products like milk protein are shown as antihypertensive properties. ACE peptide, valyl-prolyl-proline and isoleucyl-prolyl-proline peptides was observed that having antihypertensive activity in rats. A case study on casein hydrolysate (Ameal Peptide) lowered the blood pressure by -7.3mm Hg in 40 days. [15]

A milk fermented along with Enterococcus faecalis CECT 5727 in which the identified peptides LHLPLP and LVYPFPGPIPNSLPQNIPP, showed angiotensin converting enzyme-inhibitory (ACEI) activity.

Lactobacillus casei spp. Pseudoplantarum was fermented with soy protein where F1 and F2 peptides are obtained they shows ACE inhibitory properties. [16]

Peptides produces by Genetic Recombination

One of the most useful technique in microbiological geniting engineering is rDNA technique where peptides are produced at low cost with high yield. Antihypertensive peptide multimer (AHPM) was prepared using in expression in genetic material of E. coli. Its successfully expressed that E. coli having peptides which shows antihypertensive activity. [17,18]

Peptides as anti-inflammatory Agent

A study on β-hairpin hybrid peptides based upon progetrin-1, bovine lactoferricin and cecropin. A observed that contain optimum Anti-inflammatory activity. The LB-PG and CA-PG peptides show that kill microbial cell of gram negative and positive bacteria by penetrating the cell membrane as well as ruin the membrane envelop of bacteria. It indicates the presence of hybrid anti-inflammatory peptides. [19]

One of a study of phospholi-pase-A have fractionated almost 1 kg of freeze-dried bee venom and tested all the fractions for anti-inflammatory activity. It shows activity associated with peptides fraction. The venom of honey bee, Apis mellifira, is useful

in certain arthritic and rheumatoid and other inflammatory conditions. [20]

Recent study showed that cationic antimicrobial peptide having a property to treat acne vulgaris. The lipoteichoic acid was responsible for inhibit the secretion of proinflammatory cytokinin like TNF alpha and IL-1, This is useful for preparation of novel anti-inflammatory agent. [21]

rats. The significant change was observed in which TC, LDL, TG and VLDL level was highly affected. [24]

One of the studies reported that olive seed peptides having a capability to reduse the HMG co-reductase endogenously. By using in-vivo methods on cholesterol rich male and female mice. Peptides as Immunomodulatory Agents. Protein and peptides are very useful to develop immune response and immune

Name of Peptide	Anti-inflammatory properties
cationic peptides	INHIBITS LPS- and LTA-stimulated production of pro-inflammatory cytokines by macrophages
Cationic peptides obtained from endotoxin-neutralizing proteins	Inhibit TNF-α release from LPS-stimulated macrophages stage
Synthetic cationic peptide A	Decreases mRNA expression of iNOS and TNF-α in LPS-stimulated macrophages
Cecropin-melittin hybrid (CEMA)	Inhibits the LPS-induced gene expression of TNF-α and IL-1 in macrophages
Cathelicidin peptide human CAP18	Suppress LPS-induced TNF-α mRNA and protein expression
MX-594AN and MIGENIX peptides	Inhibit the release of inflammatory cytokines such as IL-1 and TNF-α in human peripheral blood lymphocytes
LL-37 peptide	Down-regulates genes of inflammatory mediators (e.g. macrophage-inflammatory protein and IL-12)
Cecropin-melittin hybrid (CEMA) peptide	Induces the expression of anti-inflammatory cytokine TGF-β receptor in macrophages
Cathelicidin PR-39 peptide	Inhibits phagocyte NADPH oxidase activity and limits related pro-inflammatory responses

List of peptides having anti-inflammatory properties [28,30,31]

Peptides as lipid lowering properties

It has been reported that red ginseng acidic polysaccharide (RGAP), isolated from red ginseng, displays anti-hyper lipidemic potential using hyper lipidemic rats induced by Triton WR1339 or corn oil injected IV. It shows that the level of non-esterified fatty acid is decrees significantly. [22]

One of the studies reported that naturally occurring serratia displays antihyperlipidemic properties in which FR177391 peptide enhances differentiation of mouse 3T3-L1 fibroblasts to adipocytes and decreses the circulating levels of triglyceride in C57BL/KsJ-db mice. This study was done in non-insulin-dependent diabetes mellitus animal model specifically. [23] Previous studies on Soy bean (Glycine max) has been reportedto have useful pharmacological effects on various cardio vascular disease. This study was designed to estimation of the effect of raw methanol seed extract of Glycine max (MEGM) on the lipid profiles of ad-libitum high-cholesterol-fed male albino wister

tolerance. In one of the studies shown that B or T-cell epitopes and their conformational constraints was useful to synthesize Immunomodulatory agent. It was useful in recovery of autoimmune disease like Rheumatoid arthritis, multiple serosis, lupus and HIV infections. [25,26,27]

Peptides as antimicrobial agents

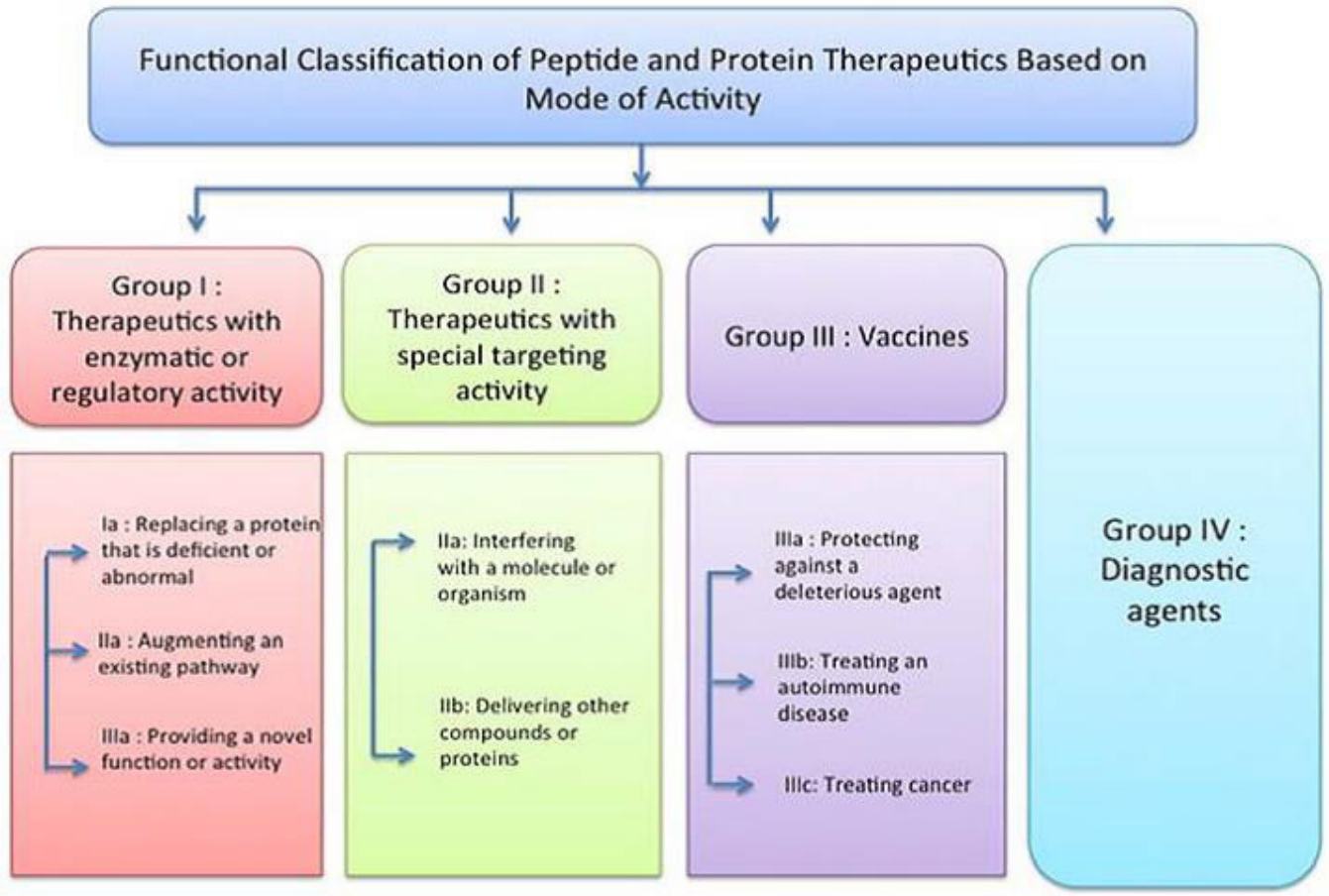
Marine derived peptides and proteins also displays the antimicrobial properties in various researches. They exhibits various physiological functions, kills bacteria's, pathogens and variety of microbial cells.[28,29] We have a list of antimicrobial potentials that is derived from marine soure:

Name of Protein	Source of Peptide	Protein Type	Mechanism of Action
Hemocyanin protein	Mollusk: *Concholepas concholepas, Megathura crenulata, Fissurella latimarginata*	Metalloprotein	Immune response against certain cancers without side effects; interact with T cells, monocytes, macrophages, and nuclear lymphocytes to improve the host immune responses
Lectin protein	*Clam: Crenomytilus grayanus, Mytilus trossulus, Fissurella latimarginata*	Glycoprotein	C-type lectins play a important role in carbohydrate recognition during immune response. Lectins have been displays as pathogenic recognizing receptors from marine invertebrates. MTL promotes the expression of proinflammatory cytokines (TNF-α and IFN-γ), but decrease the hyper-expressions of anti-inflammatory cytokine activity (IL-10).
Taurine protein	Clam: *Tapes philippinarum*	2-Amino ethane sulfonic acid	Cytoprotective and immunomodulatory effects in immune cells including lymphocytes, monocytes, and neutrophils; accumulation of phagocytes, contact with pathogens, activated cells (neutral and macrophages) produce toxic oxidants and various antibacterial substances using the peroxidase system and ruin the pathogens; scavenger to remove harmful substances from the cells and protect them from oxidative stress like modulation of the immune system by activating NF-κB and sensitise PPAR-g.

List of Naturally occurring peptides used as Immunomodulatory agent

Name of peptides	Source	Application
Clavanin A	Tunicate: styelaclava	Kills Gram positive and Gram negative drug resistant bacteria.
Definsin	Oyster:crassostera gigas and Mytilus edulis	Disrupts the Membrane of microbial pathgens, knowm as antimicrobial pepetides.
Crustin	Crusteacean:Paneous monodon,Fenneropanaeus chinensis	Antimicrobial and antibacterial activity.
Mytilin	Mullusk: Mytilus edulis	Strong antimicrobial activity
Mytimycin	Mytilus edulis and M. galloprovincialis	Antibacterial and antifungal activity
Lysin peptide	Salmo salar fish	Potent antimicrobial activity
Peptide Pt5	Danio rerio	Antimicrobial activity
TP3 and TP4	Oreochromis niloticus	Bacteriostatic and antimicrobial activity
Scygonadin	Scylla serrata	Antimicrobial activity

Peptides as antimicrobial agents



Overview of the classification /mode of activity-based and Functions of therapeutic proteins and peptides

Conclusion

Proteins and peptide modified Drugs plays vital role in treatment of various disease and disorders and becoming a very important class of therapeutic agents and can exchange various existing organic based pharmaceuticals in future. Peptides having a wide range of therapeutic area along with less side effects comparing synthetic organic drugs and peptides can easily produce by various biotechnological methodologies like Fermentation, rDNA technology and others. Their need in the clinical and therapeutic regions has intensified the outcomes for their useful and effective delivery by application of non-invasive system. After a few decades of research, we can choose from a rapidly growing arsenal of various peptide-based transfection systems each suitable for a selective application. Predictions tools are very crucial for planning, designing and synthesis of novel therapeutically active peptides. Prediction accuracy depends on the authentic information contained within descriptors. [30,31] In Future we expect that new emerging peptide technologies for multifunctional peptides, cell penetrating peptides and peptide drug conjugates, will help broaden the applicability of peptides as therapeutics.

References

1. Abbara A, Jayasena CN, Christopoulos G (2015) Efficacy of kisspeptin-54 to trigger oocyte maturation in women at high risk of ovarian hyperstimulation syndrome (OHSS) during in vitro fertilization (IVF) therapy. J Clin Endocrinol Metab 100: 3322–31.

2. FDA Guidance for industry (2017) ANDAs for certain highly purified synthetic peptide products that refer to listed drugs of recombinant DNA origin.

3. Dhanda SK, Usmani SS, Agrawal P, Nagpal G, Gautam A, et al. (2017) Novel in silico tools for designing peptide-based subunit vaccines and immunotherapeutic. Brief Bioinform 18: 467-78.

4. Leader B, Baca QJ, Golan DE (2008) Protein therapeutics: a summary and pharmacological classification. Nat Rev Drug Discovery 7: 21-39.

5. Gaulton A, Bellis LJ, Bento AP, Chambers J, Davies M, et al. (2012) ChEMBL: a large-scale bioactivity database for drug discovery. Nucleic Acids Res 40: D1100-7.

6. Walther A, Riehemann K, Gerke V (2000) A novel ligand of the formyl peptide receptor: annexin I regulates neutrophil extravasation by interacting with the FPR. Mol Cell 5: 831-40.

7. WL Zhu, D Czyzyk, SA Paranjape, LG Zhou, A Horblitt, et al. (2000) Glucose prevents the fall in ventromedial hypothalamic GABA that is required for full activation of glucose counterregulatory responses during hypoglycemia, Am. J. Physiol-Endocrinol. Metab. 298: E971–7.

8. O Chan, S Paranjape, D Czyzyk, A Horblitt, WL Zhu, et al. (2011) Increased GABAergic output in the ventromedial hypothalamus contributes to impaired hypoglycemic counter-regulation in diabetic rats, Diabetes 60: 1582-9.

9. P Seoane-Collazo, J Ferno, F Gonzalez, C Dieguez, R Leis, et al. (2015) Hypothalamic-autonomic control of energy homeostasis, Endocrine 50: 276-91.

10. GJ Taborsky, TO Mundinger (2012) Minireview The role of the autonomic 0nervous system in mediating the glucagon response to hypoglycemia, Endocrinology 153: 1055–62.

11. ASP Jansen, JL Hoffman, AD Loewy (1997) CNS sites involved in sympathetic and parasympathetic control of the pancreas: a viral tracing study, Brain Res 766: 29–38.

12. Jakala P, Vapaatalo H (2010) Antihypertensive peptides from milk proteins. Pharmaceuticals 3: 251–72.

13. Meisel H (1998) Overview on milk protein-derived peptides. Int Dairy J 8: 363-73.

14. Yamamoto N, Takano T (1999) Antihypertensive peptides derived from milk proteins. Nahrung 43: 159–64.

15. Shin JoungRho, Ji-SooLee, Yong Il Chung, Young-WanKim, Hyeon Gyu Lee (2009) Purification and identification of an angiotensin I-converting enzyme inhibitory peptide from fermented soybean extract. Process Biochem 44: 490-3.

16. Feng-Juan Li, Li-Jun Yin, Yong-Qiang Cheng, Kohji Yamaki, Junfeng Fan, et al. (2009) Comparison of angiotensin I-converting enzyme inhibitor activities of pre-fermented Douchi started with various cultures. Int J Food Eng 5: 10.

17. Sachie Ibe, Keiko Yoshida, Kaoru Kumada, Shigeko Tsurushiin, Tadasu Furusho, et al. (2009) Antihypertensive effects of natto, a traditional Japanese fermented food, in spontaneously hypertensive rats. Food Sci Technol Res 15: 199-202.

18. Kaori Inoue, Takanobu Gotou, Hirokuni Kitajima, Seiichi Mizuno, Takeshi Nakazawa, et al. (2009) Release of antihypertensive peptides in miso paste during its fermentation, by the addition of casein. J Biosci Bioeng 108: 111-6.

19. Vallabha VS, Tiku PK (2014) Antihypertensive peptides derived from soy protein by fermentation. Int J Pept Res Ther 20: 161-7.

20. Lv GS, Fu XY (2003) Expression of milk-derived antihypertensive peptide in escherichia coli. J Dairy Sci 86: 1927-31.

21. YK Kim, S Yoon, DY Yu, B Lönnerdal, BH Chung (1999) Novel Angiotensin-I-converting enzyme inhibitory peptides derived from recombinant human as1-casein expressed in Escherichia coli. J Dairy Res 66: 431-9.

22. Shengqi Rao, Yujie Su, Junhua Li, Zhenzhen Xu, Yanjun Yang (2009) Design and expression of recombinant antihypertensive peptide multimer gene in Escherichia coli BL21. J Microb Biot 19: 1620-7.

23. Hernandez-Ledesma B (2011) Antihypertensive peptides: Production, bioavailability and incorporation into foods. Adv Colloid Interface Sci 165: 23-35.

24. Endo A (1985) Compactin (ML-236B) and related compounds as potential cholesterol-lowering agents that inhibit HMG-CoA reductase. J Med Chem 28: 401-5.

25. Bunji Sato, Hidenori Nakajima, Takashi Fujita, Shigehiro Takase, Seiji Yoshimura, et al. et al. (2005) FR177391, a new anti-hyperlipidemic agent from Serratia. I. Taxonomy, fermentation, isolation, physico-chemical properties, structure elucidation and biological activities. J Antibiot 58: 634–9.

26. Van-Burden TP, Robinson EC (1981) Formation of complexes between protein and tannin acid. J Agric Food Chem 1: 77–82.

27. BO Obadoni, PO Ochuko (2001) Phytochemical studies and comparative efficacy of the crude extracts of some homeostatic plants in Edo and Delta States of Nigeria. Global J of Pure and Appl Sci 8: 204–7.

28. Bohm, Bruce A Koupai-Abyazani, Mohammed R (1994) Flavinoids and condensed tannins from leaves of Hawaiian Vaccinium Vaticulum and V. calycintum, Pacific Sci 48: 458–62.

29. YiFan Liu, Xi Xia, Liang Xu, YiZhen Wang (2013) Design of hybrid β-hairpin peptides with enhanced cell specificity and potent anti-inflammatory activity biomaterial 34: 237-50.

30. Gough M Hancock, RE Kelly NM (1996) Antiendotoxin activity of cationic peptide antimicrobial agents. Infect Immun 64: 4922-6.

31. Scott MG, Davidson DJ, Gold MR, Bowdish D, Hancock RE (2002) The human antimicrobial peptide LL-37 is a multifunctional modulator of innate immune responses.J Immunol 169: 3883-90.