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A systematic review of therapeutic proteins as a promising approach to treat various diseases

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Abstract

Proteins if said as 'magic molecules' will not prove false because of a varied play it can deal with in view of health sector. In the past couple of decades, therapeutic proteins have gained significance as therapy for a wide range of diseases like cancer, cardiovascular, diabetes and some other diseases. Moreover, recently USFDA protein therapeutic products are also playing an important role in this concern. Whereas therapeutic application of whey protein is rapidly on its way to be proved helpful. The thing of concern to use of these therapeutic proteins for the treatment of various diseases is a proper and rational formulation of protein-based therapeutics. Advancements in the field of biotechnology have increased and facilitated the production of therapeutically significant proteins to combat various potentially fatal diseases. However, there are still a few factors that hinder the efficient use of these valuable therapeutics. For instance, the oral route of administration faces proteolysis and/or hydrolysis in the GIT, whereas some drugs go through the hepatic first pass effect or show poor distribution. Therefore, a better insight into the routes of administration and the drug absorption mechanisms (paracellular, transcellular, and carrier mediated) is essential. This review has explained all the possible factors that are linked with the basis of therapeutic proteins, including their introduction, classification, their importance in the healthcare system, and possible challenges that are currently being faced by scientists during the development of protein-based therapeutics.

Keywords: Therapeutic proteins; Diseases; Classification; Formulation aspects

1. Introduction

Proteins which are engineered in the laboratory for pharmaceutical use are referred as therapeutic proteins. Peptides and proteins are known to have great therapeutic potential against several diseases and syndromes. The current progress in the field of pharmaceutical biotechnology has increased the value and number of protein and peptide based therapeutics in the market. The FDA has approved many recombinant proteins as biotechnology medicines, antibody-drug conjugates, vaccines, enzymes, natural/recombinant cytokines, and interferons. [1]

Recent advances in biotechnology allow the selection and the preparation of novel macromolecular compounds such as peptides, proteins, and DNA analogues (produced by Hybridoma cell technology and Recombinant DNA technology) to be used as drugs (e.g., hormones, monoclonal antibodies, vaccinations) for therapeutic purposes. these recombinant therapeutic proteins are also known as biotechnological therapeutics because they are used for multiple purposes, including diagnosis, prophylaxis, disease management, and/or cure. Protein and peptides are increasingly recognized as potential candidates for the development of new therapeutics for variety of human ailments. Due to their relatively specific mode of action, proteins and peptides can be administered at comparatively low doses for therapeutic effects.[2]Therapeutic proteins are increasingly prominent because they have proven to be effective in treating many

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potentially fatal diseases like diabetes, heart disorders, and cancer. Therapeutic protein drugs are an important class of medicines serving patients most in need of novel therapies. Due to their large applications in pharmaceutical industries, they will replace many existing organic based pharmaceuticals.

The most common route for administration of protein and peptide drug delivery is parenteral, although other routes are also have been tried with varying degree of success. Routes such as intranasal, transdermal, buccal, intraocular, rectal, vaginal and pulmonary route deliver the drug to the systemic circulation while avoiding transit through the digestive system.[3]

Table 1 Advantages and disadvantages of therapeutic proteins. [4]

Advantages	**Disadvantages**
Broad range of targets	Limited oral bioavailability
Low toxicity	Elevated production costs
High chemical and biological diversify	Short half-life and rapid clearance
High potency and selectivity	Low metabolic stability
Good efficacy, safety, and tolerability	Poor membrane permeability
Low accumulation in tissues	Tendency for aggregation
	They can contain immunogenic sequences

Interestingly, proteins have now been proven effective even as vaccines that help stimulate the body's natural defense mechanism for immunogenic response. Therapeutic proteins have acquired a central role in drug discovery and development with enhanced safety profiles for human use, as both proteins and peptides have proven therapeutical outcome against various disease conditions.

Applications of therapeutic proteins [4]

- Enzymes are used for treating enzyme-deficiencies in the body.
- Supplementation of blood coagulation factors.
- Therapeutic antibodies used for treating various diseases like different tumours, cardiovascular diseases, inflammatory diseases, macular degeneration, sclerosis multiplex, viral infections or for preventing rejection following transplantations.
- Virus-like particles usually given in the form of vaccine contain a protein–like part of a virus and are able to generate immune response.
- Peptides hormones like insulin and glucagon use in treatment of diseases like diabetes and hyperglycemias.

1.1. Classification of therapeutic proteins

Both proteins and peptides are recognized to have numerous effective capabilities, but they vary in terms of their properties. Therapeutic proteins are categorized in terms of their functions and therapeutic applications. They are placed in groups of either approved by FDA (Group I and II) or investigated in vivo/in vitro (Group III and Group IV), as summarized in Figure 1.

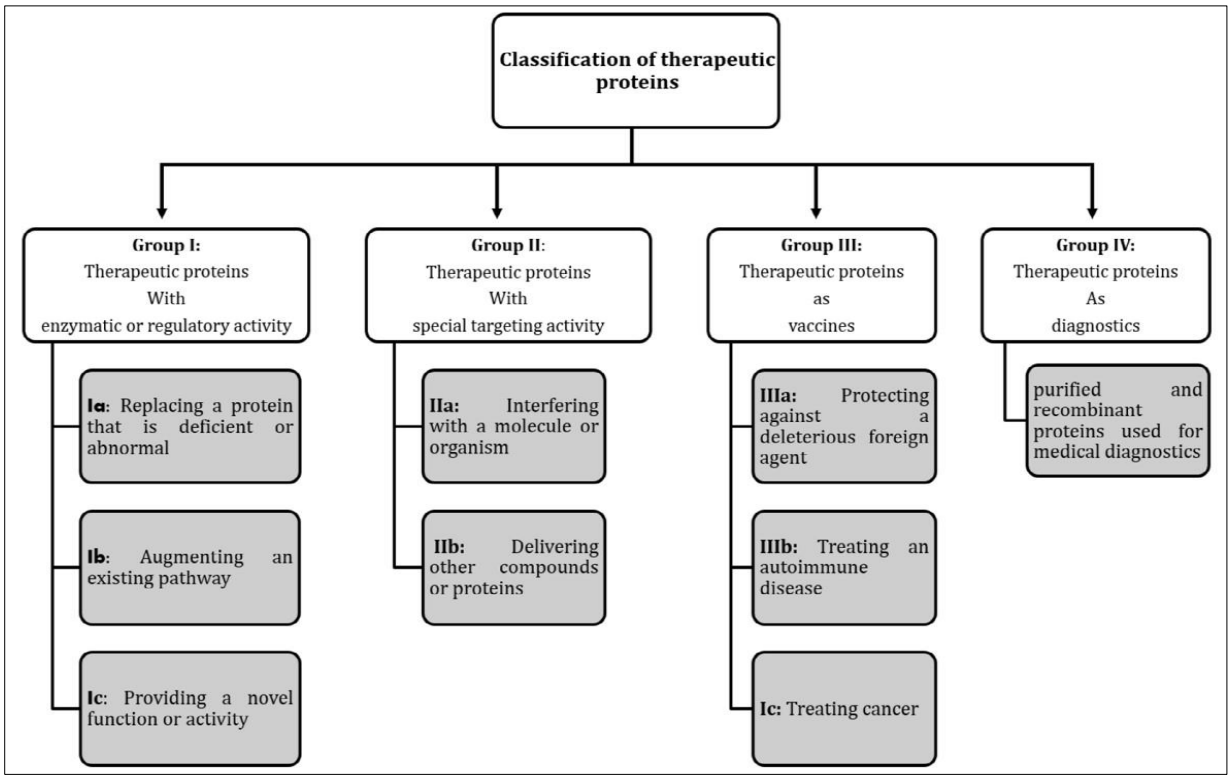

Figure 1 Classification of Therapeutic Proteins [1]

1.2. Formulation of therapeutic proteins

The formulation is considered to be more complicated as compared with the formulation of other conventional therapeutic agents. For this reason, product preformulation is recognized as a critical stage in the formulation of proteins and peptides as therapeutics. The three-dimensional structure of proteins is considered to be the major determinant of their proper functioning. Moreover, changes in external and/or internal variables including temperature, pH, and chemical interaction/modification or mutation may lead to processes like denaturation, aggregation, or precipitation, causing destabilization of the protein structure and affecting its functioning.[5]

Protein aggregation is known to lead to probable immunogenicity in patients and is considered one of the major factors that need to be monitored carefully from the production until the storage stage of therapeutic protein development. Another degradation pathway that may influence protein stability during the formulation of therapeutic proteins is protein oxidation.

Like protein aggregation, the oxidation of therapeutic proteins can result in an alteration of the structure of these proteins, which may further lead to modifications in their secondary, tertiary, and quaternary structure. These factors are controlled by adopting suitable and appropriate formulations and protein carrier particulate systems. Most of the therapeutic proteins are temperature and pH sensitive and they are rapidly degraded when given orally. These shortcomings have been overcome by various chemical and physical modifications. Immunogenicity and instability of therapeutic proteins can be stopped by modifying the protein structure via alteration of amino acid sequences or optimizing the formulation of therapeutic proteins using different types of polymers.

2. Challenges in development of therapeutic proteins

In the past several decades, advances and developments in DNA-based genetic engineering technologies have made it possible to develop and synthesize a large number of therapeutic proteins to combat a corresponding variety of life-threatening diseases and syndromes. Designing oral peptide and protein delivery systems has been a persistent challenge to pharmaceutical scientists because of their several unfavorable physicochemical properties including large molecular size, susceptibility to enzymatic degradation, short plasma half-life, ion permeability, immunogenicity, and the tendency to undergo aggregation, adsorption, and denaturation.[6]The delivery of protein treatments is being improved through the development of various methods, but there are some safety concerns specific to protein products

that are not generated by low molecular weight medicines.[7]In the following subsections, we discuss these challenges and ways to make therapeutic proteins the ideal therapeutics.

2.1. Developmental challenges

From the discovery of new molecules to their entrance into the pharmaceutical market, approximately 10 years are required, but the probability of success (POS) is not a guarantee. For small molecules, the POS is 6%–7%, whereas for monoclonal antibodies and fusion proteins the POS is about 17%.[8] Therefore, it is important that molecules that have a maximum POS be selected.

2.2. Safety and immunogenicity issues

The most important feature of these therapeutic proteins is their safety and clinical efficacy, which can be achieved by a combination of several factors, including disease state, target biology, potency, safety margin, dosing, and selection of patient population. The following are some factors that should be considered in terms of safety and immunogenicity: a) molecules that provide maximum margin of safety; b) the delivery route; c) prolonged half-life; d) tissue distribution; e) stability and enzymatic degradation; and f) solubility of molecule under development. the consequences of an immune response to protein-based biopharmaceuticals range from temporary appearance of antibodies without clinical significance to severe life-threatening complications like anaphylaxis, neutralization of the effectiveness of life-saving or highly effective therapies, or neutralization of endogenous proteins with non-redundant functions, decrease in efficacy, and induction of autoimmunity, including antibodies to the endogenous form of the protein.[10]

2.3. Protein stability

Protein-based biopharmaceuticals are prone to physical or chemical instabilities. Therapeutic proteins tend to aggregate when stored under high concentration conditions as required for their usage. Aggregation tends to decrease their overall activity and sometimes elicit immunological reactions. Another factor that may influence the stability of therapeutic proteins is temperature.Most often, extracted proteins are stored for an extended period of time to maintain their activity and original structural integrity.

Usually, proteins are best stored at ≤4°C. Storage at room temperature often leads to the degradation of therapeutic proteins. Several strategies are being applied to increase the stability of therapeutic proteins. The first approach is to alter the amino acid sequences in the protein structure. The second one is to optimize the formulation of therapeutic proteins.[9] Thermo sensitive polymers have also shown to increase the stability of therapeutic proteins. Biodegradable polymers have been intensively evaluated for the successful delivery of a variety of therapeutic proteins. Protein stability can also be increased using nontoxic nano-structured materials along with development of molecules that are aggregation-resistant and incorporation of formulation additives that prevent aggregation.[10]

2.4. Protein degradation

Protein degradation is another challenge that occurs at different stages throughout the entire process of development and delivery of the drug to its desired sites. If certain conditions are not maintained during their storage, therapeutic proteins may not function properly.

Proteins can lose therapeutic activity as a result of proteolysis, aggregation, and suboptimal buffer conditions. Proteins can lose therapeutic activity as a result of proteolysis, aggregation, and suboptimal buffer conditions. It is important to understand and quantify various routes of chemical degradation such as oxidation, deamidation, chemical cross-linking, disulfide modifications, and fragmentation.[11]Several strategies are being used to prevent the degradation of therapeutic proteins. The most common one is the encapsulation of therapeutic proteins with inert and biocompatible polymers. Protein degradation can also be prevented by co-administration of enzyme inhibitors with therapeutic proteins. Microencapsulation techniques, such as spray drying, phase separation and emulsion techniques have been extensively used for the encapsulation of drugs and proteins. Apart from using polymers for microencapsulation techniques, lipids have also been used to encapsulate protein, involving supercritical fluid technology, Dynasan® 114 and Gelucire® 50-02, for the encapsulation of a model protein, bovine serum albumin. .Another study, involving the encapsulation of insulin, was demonstrated by Caliceti et al.[12]

2.5. Protein–excipient interactions

During the formulation development of therapeutic proteins, protein–excipient interactions must be evaluated to enhance the overall stability of protein therapeutics and minimize the chances of any kind of immunogenicity.The polymer used for the incorporation of therapeutic proteins must be inert, biocompatible, and most preferentially

biodegradable in nature. Different types of techniques are being used by pharmaceutical scientists to evaluate the protein excipient interactions.

2.6. Metabolism and elimination

A major factor that limits the usefulness of these substances for their intended therapeutic application is that they are easily metabolized by plasma proteases when they reach the peripheral circulation. Hepatic metabolism and rapid elimination is a major roadblock to the clinical application of therapeutic proteins. Several efforts have been made to circumvent these hurdles. These efforts include the non-invasive delivery of therapeutic proteins through routes (other than the oral route) that bypass the hepatic metabolism of the administered therapeutic proteins. Moreover, invasive delivery of therapeutic proteins is also an alternative tool to prevent the hepatic first-pass metabolism.

Furthermore, the majority of therapeutic proteins have a short biological half-life. This problem might be overcome by encapsulating and/or conjugating desired therapeutic proteins with biocompatible polymers, like polyethylene glycol to extend the half-life of therapeutic proteins. Recently, IL-1Ra, a naturally occurring anti-inflammatory antagonist of pro-inflammatory cytokines, has been successfully encapsulated in PF127. In vitro and in vivo studies have shown that PF127 significantly prolongs the sustained release of IL-1Ra, and maintains in vitro stability, in vivo bioactivity, and therapeutic potentials.[13]

3. Therapeutic proteins used in treatment of various diseases

3.1. Peptides used in cancer treatment

Cancer is characterized by uncontrolled division of cells and the ability of these cells to invade other tissues leading to the formation of tumour mass, vascularization, and metastasis.[14]Discovery of several protein/peptide receptors and tumour-related peptides and proteins is expected to create a new wave of more effective and selective anticancer drugs in the future, capturing the large share of the cancer therapeutic market.[15,16]The biologics treatment option against cancer includes the use of proteins, mono-clonal antibodies, and peptides.

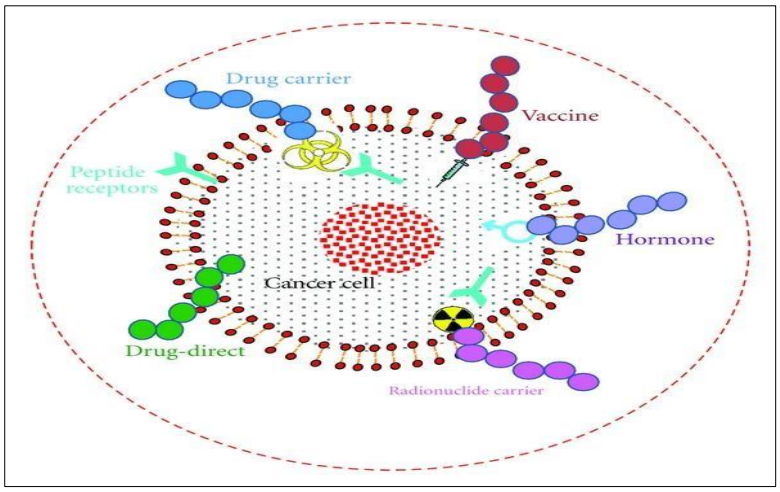

Figure 2 Different possible treatment options of cancer using peptides. Peptides can be used as anticancer drug, cytotoxic drug carrier, vaccine, hormones, and radionuclide carrier.[17]

3.1.1. Anticancer Peptides

Direct use of peptide as a therapeutic agent to treat cancer is gaining momentum in the recent years. Anticancer activity of different peptides is attributed to a variety of mechanisms that restrict tumour growth. The mechanism involves the inhibition of angiogenesis, protein-protein interactions, enzymes, proteins, signal transduction pathways, or gene expression.[18, 19]Another category of anti-cancer peptides is peptide antagonists which can preferentially bind to a known receptor.[20] Moreover proapoptotic peptides mediate significant induction of apoptosis (programmed cell death) in tumours.[21]Angiogenesis involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels. Angiogenesis requires the binding of signaling molecules, such as vascular endothelial growth factor (VEGF) to receptors on the surface of normal endothelial cells. When VGEF and other endothelial growth

factors bind to ApoA-I, the major protein component of the particle, is predominantly responsible for the anti-atherogenic.

Recently it was found that angiotensin can stop lung cancer tumour growth in mice by inhibiting blood vessels.[22]Scientists have designed peptides to target the protein-protein interface of a key enzyme in DNA synthesis crucial for cancer growth.[34] The peptides act by a novel inhibitory mechanism and curb cancer cell growth in drug resistant ovarian cancer cells. These octapeptides specifically target the protein-protein interface of thymidylate synthase. Thymidylate synthase is composed of two identical polypeptide chains; that is, it is a homodimer. The peptides stabilize the inactive form of the enzyme, show a novel mechanism of inhibition for homodimeric enzymes, and inhibit cell growth in drug sensitive and resistant cancer cell lines.[23]Cisplatin, cisplatinum, or cis-diamine dichloroplatinum (II) is the first member of a class of platinum-containing anti-cancer drugs. These platinum complexes react in vivo, binding to and causing cross linking of DNA, which ultimately triggers apoptosis (programmed cell death). Recently, Pt (IV)-peptide conjugates were found to be good inhibitors of cellular proliferation. Different mechanisms of action of anticancer peptides are presented in fig. 3.

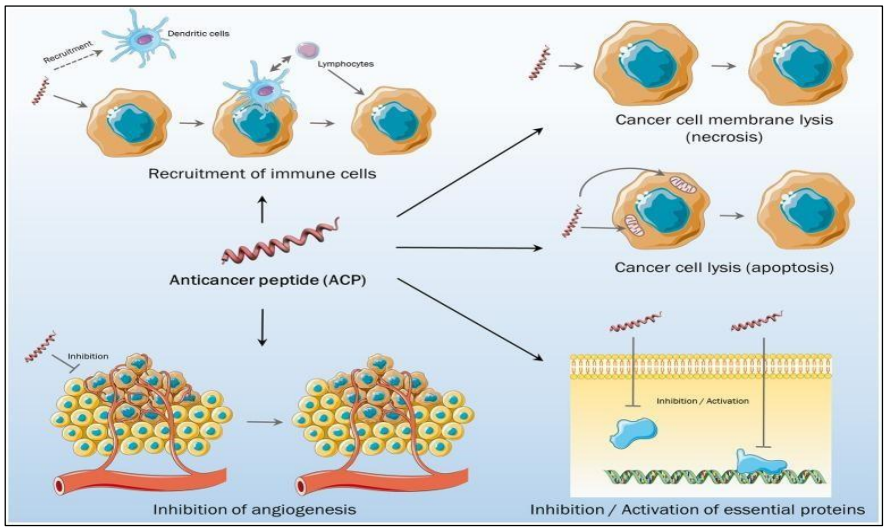

Figure 3 Different mechanisms of action of anticancer peptides.[24]

3.1.2. Peptide Hormones: LHRH Agonists and Antagonists

Table 2 LHRH agonists and new generation antagonists available in the market Table 2

Peptide	**Indications**
Buserelin agonist	Prostate cancer
Gonadorelin agonist	Cystic ovarian disease, agent for evaluating hypothalamic -pituitary gonadotropic function
Histrelin agonist	Prostate cancer, breast cancer
Leuprolide agonist	Prostate cancer, breast cancer
Nafarelin agonist	Treat symptoms of endometriosis, central precocious puberty
Triptorelin agonist	Prostate cancer, breast cancer
Goserelin agonist	Prostate cancer, breast cancer
Abarelix antagonist	Prostate cancer
Cetrorelix antagonist	Prostate cancer, breast cancer
Degarelix antagonist	Prostate cancer
Ganirelix antagonist	Fertility treatment

Depot formulations of LHRH agonists such as buserelin, leuprolide, goserelin, and triptorelin have been developed for more efficacious and more convenient treatment of patients with prostate cancer.[19,20,21] Administration of these peptides causes down regulation of LHRH receptors in the pituitary, leading to an inhibition of follicle-stimulating hormone (FSH) and LH release, and a concomitant decrease in testosterone production. This offered a new method for androgen deprivation therapy in prostate cancer patients. Discovery of LHRH antagonists resulted in therapeutic improvement over agonists as they cause an immediate and dose-related inhibition of LH and FSH by competitive blockade of the LHRH receptors. To date, many potent LHRH antagonists are available for the clinical use in patients. Subsequently, new generation LHRH antagonists such as abarelix and degarelix have been approved for human use.[25,26] A list of LHRH agonists and antagonists available in the market is shown in Table 2.

3.1.3. Peptide as Radionuclide Carrier Somatostatin Analogues in Cancer Therapy and Peptide Receptor Radionuclide Therapy (PRRT)

Potent analogues of somatostatin including octreotide (sandostatin) have been developed for the treatment of acromegaly, gigantism, thyrotropinoma, diarrhea and flushing episodes associated with carcinoid syndrome, and diarrhea in patients with vasoactive intestinal peptide-secreting tumors (VIPomas).[27] Similarly, another long-acting analogue of somatostatin, lanreotide (somatuline), is used in the management of acromegaly and symptoms caused by neuroendocrine tumors, most notably carcinoid syndrome and VIPomas.[28]Most neuroendocrine tumors (NETs) feature a strong over expression of somatostatin receptors, mainly of subtype 2. The density of somatostatin receptors is vastly higher than on non-tumor tissues. Therefore, somatostatin receptors are attractive targets for delivery of radioactivity via radiolabeled somatostatin analogs. The SST2 has been shown to internalize into the cell in a fast, efficient, and reversible manner after specific binding of a receptor agonist. This molecular process is likely to be responsible for the high and long-lasting uptake of radioactivity in the target cell after binding of the radiolabeled somatostatin analogue. Octreoscan and NeoTect (tc-99 depreotide) are the only radiopeptide tracers on the market approved by the Food and Drug Administration.[29,30] Octreotide scan or octreoscan is a type of scintigraphy used to find carcinoid and other types of tumors and to localize sarcoidosis. Octreotide, a drug similar to somatostatin, is radiolabeled with indium-111 and is injected into a vein and travels through the bloodstream. The radioactive octreotide attaches to tumour cells that have receptors for somatostatin. A radiation-measuring device detects the radioactive octreotide and makes pictures showing where the tumour cells are in the body. NeoTect is a radioactive imaging test used to evaluate certain lung lesions in patients who test positive for lung lesions using other imaging tests (e.g. CT or MRI) and have been diagnosed with cancer or have a strong likelihood of cancer. NeoTect identifies certain cells that maybe associated with lung cancer and sometimes with other conditions.[32]Radiolabeled somatostatin analogues generally comprise three main parts:a radioactive element(111In, 90Y, or 177Lu), a chelator (such as DTPA or DOTA), and a cyclic octapeptide (such as octreotide) . These radiopeptides can be injected into a patient and will travel throughout the body binding to carcinoid tumour cells that have receptors for them .Once bound, these radiopeptides emit radiation and kill the tumor cells they are bound to as shown in Figure 4.

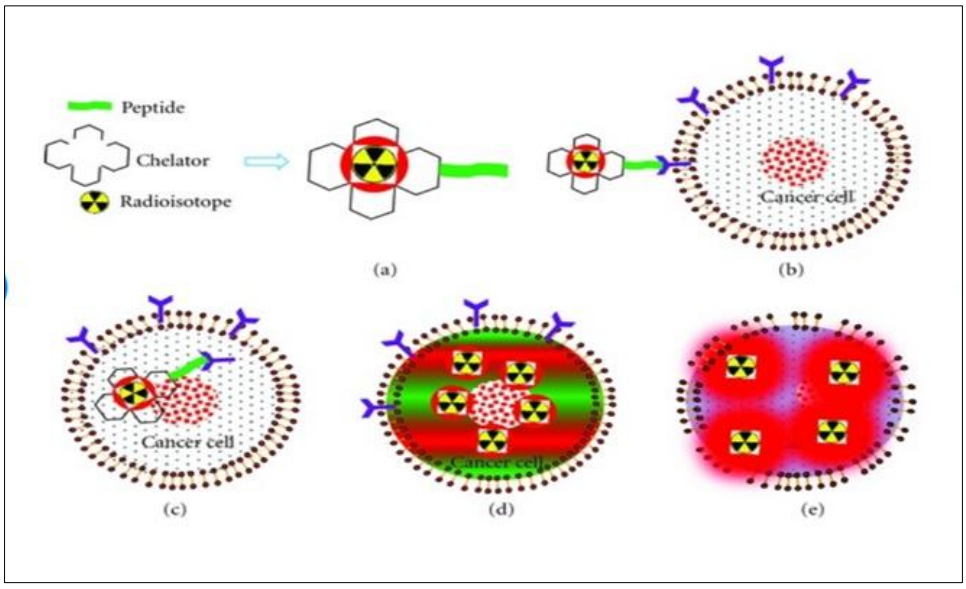

Figure 4 Radiopeptides binding to tumour cells and action

3.1.4. Peptide Vaccines

Active immunization seems to be one of the promising strategies to treat cancer though many approaches based on the employment of immune cells or immune molecules have been studied.[31,32] This method of treating cancerous cells relies on vaccines consisting of peptides derived from the protein sequence of candidate tumor-associated or specific antigens.[31]

Tumor cells express antigens known as tumor-associated antigens (TAAs) that can be recognized by the host's immune system (T cells). These TAAs can be injected into cancer patients in an attempt to induce a systemic immune response that may result in the destruction of the cancer growing in different body tissues. This procedure is defined as active immunotherapy or vaccination as the host's immune system is either activated de novo or restimulated to mount an effective, tumor-specific immune reaction that may ultimately lead to tumor regression (Figure 3). Any protein/peptide produced in a tumor cell that has an abnormal structure due to mutation can act as a tumor antigen. Such abnormal proteins are produced due to mutation of the concerned gene. The peptide vaccines are relatively less expensive, easy to manufacture and manipulate, are of defined structure, and being synthetic in nature do not have a problem of batch to batch variation. The major disadvantage of the peptide vaccines is their weak immunogenicity.

3.1.5. Peptide as Cytotoxic Drug Carrier

A peptide can be conjugated to a cytotoxic drug to deliver it to a cancer cell expressing the corresponding peptide receptor. Such peptides are known as cell targeting peptides as they can specifically target a cell expressing its receptor. Cytotoxic compounds linked to analogs of hormonal peptides like LHRH, bombesin, and somatostatin can be targeted to certain tumors possessing receptors for those peptides and therefore are more selective for killing cancer cells.[33,34]For example, a potential drug candidate, AEZS-108, couples a peptide LHRH with the chemotherapeutic agent doxorubicin to directly target cells that express LH-RH receptors, specifically prostate cancer cells.[35,36]Nevertheless, these receptors provide good platform for the cell-specific delivery of chemotherapeutic agents.

Homing peptides have been successfully used as delivery vehicles to target imaging agents, drug molecules, oligonucleotides, liposomes, and inorganic nanoparticles to tumours and other tissues.[37,38,39]One drug that has been delivered using RGD and NGR peptides is the tumor necrosis factor-α (TNF-α) that has potent antitumor activity.[40,41] The antitumor activity of NGR-TNF-α was also studied in combination with various chemotherapeutic drugs: doxorubicin and melphalan as well as cisplatin, paclitaxel, and gemcitabine and compared to the efficacy of the chemotherapeutic drugs alone in various murine tumour models.[41]The results showed that targeted delivery of low doses of NGR- TNF-α to tumor vasculature increased the efficacy of various drugs acting via different mechanisms. This treatment inhibited tumor growth and prolonged the life span of tumor-bearing animals. A list of different peptide receptors, their subtypes, tumours in which these receptors are expressed, and some of the targeting agents used are depicted in Table 3.[42]The mechanism of cytotoxic effect of peptides can be understood by fig. 5.

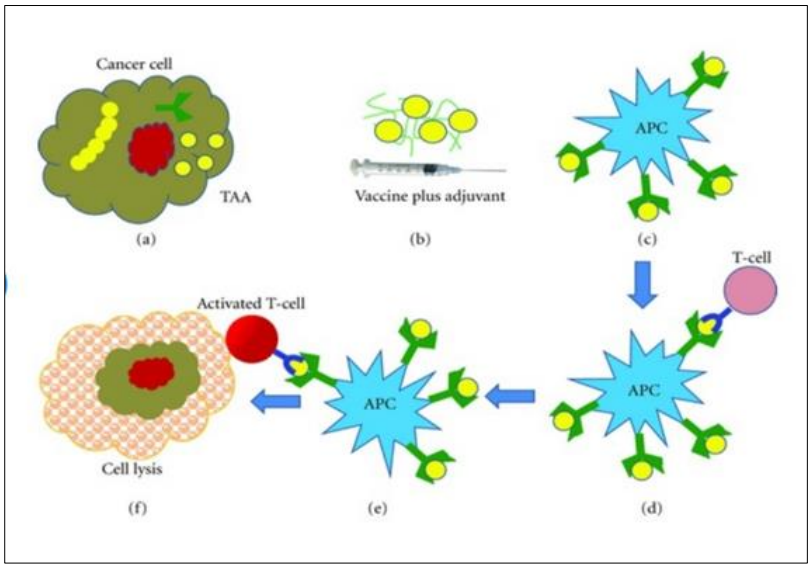

Figure 5 Cytotoxic effect of peptides and mechanism

Table 3 Different peptide receptors, their subtypes and targeting agents

Peptide Receptors	Receptor Subtypes	Expressing tumour type	Targeting agents
Somatostatin	sst1, sst2, sst3, sst4, sst5	GH-producing pituitary adenoma, paraganglioma, nonfunctioning pituitary adenoma, pheochromocytomas	Radioisotopes, AN-20 potent cytotoxic radioisotopes, 2-pyrrolinodoxorubicin, doxorubicin
Pituitary adenylate cyclase activating peptide (PACAP)	PAC1	Pheochromocytomas and paragangliomas	Radioisotopes, doxorubicin
Vasoactive intestinal peptide (VIP)	VPAC1, VPAC2	Cancers of lung, stomach, colon, rectum, breast, prostate, pancreatic ducts, liver and urinary bladder	Radioisotopes, camptothecin
Cholecystokinin (CCK)	CCK1 and CCK2	Small cell lung cancers, medullary thyroid carcinomas, astrocytomas and ovarian cancer	Radioisotopes, cisplatin
Bombesin/ Gastrin Releasing Peptide (GRP)	BB1, BB2, BB3 and BB4	Renal cell, breast, prostate carcinomas	Doxorubicin,2-pyrrolinodoxorubicin
Neurotensin	NTR1, NTR2, NTR3	Small cell lung cancer, neuroblastoma, pancreatic and colonic cancer	Radioisotopes
Substance P	NK1 receptors	Glial tumours	Radioisotopes
Neuropeptide Y	Y1-Y6	Breast carcinomas	Radioisotopes

3.2. Peptides and Peptidomimetics used in cardiovascular diseases

Cardiovascular diseases remain a leading cause of mortality and morbidity worldwide. Attempts to prevent cardiovascular diseases usually involve control and improvement of causative risk factors such as hypercholesterolemia, inflammation, hyperglycemia, obesity, insulin resistance, or high blood pressure.[43]Limitations in currently available device therapies and pharmacologic drugs in CVD has prompt new treatment modalities such peptides and their mimetics. One of the key goals of cardiovascular therapies is to reduce LDL cholesterol accumulation in the sub-endothelial space lining the artery wall, thereby preventing the progression of atherosclerosis and reducing the risk of heart attack and stroke. A plasma LDL cholesterol reduction of 1 mmol/L has been reported to reduce the risk of cardiovascular events by approximately 20%). HDL is considered to promote the removal of free cholesterol from peripheral tissue and its transport to the liver for eventual clearance.

3.2.1. Apolipoprotein Mimetic Peptides

ApoA-I, the major protein component of the HDL particle, is predominantly responsible for the anti-atherogenic properties attributed to HDL.[44] ApoA-I is critical for the process of reverse cholesterol transport and cellular cholesterol homeostasis. Several murine pre-clinical models of atherosclerosis have shown potent protective effects of ApoA-I following prophylactic and therapeutic intervention. ApoA-I is widely considered as a promising target for CVD treatment, and different therapeutic approaches have been developed to mimic its function. This peptide was also shown to possess potent anti-inflammatory, anti-oxidant, and atheroprotective effects. ApoE clears lipoproteins by LDL receptor-independent mechanisms. It also plays a crucial role in the regulation of plasma cholesterol levels.

3.2.2. SOCS1-Derived Mimetic Peptides

SOCS proteins give negative-feedback regulators of the JAK/STAT pathway, which drive the production of cytokines and inflammatory factors that affect atherosclerotic processes, including leukocyte recruitment, migration, and proliferation of vascular cells, foam cell formation and apoptosis.[45]In diabetic patients, the control of blood glucose levels is a major goal to prevent further tissue damage and cardiovascular events such as stroke, heart attack, or end-stage renal disease.

3.2.3. Incretin Mimetics

Incretin mimetic-based therapies, with particular focus on GLP-1R agonists and DPP4 inhibitors, are currently leading therapeutic agents available for type 2 diabetes treatment. As peptidomimetics, GLP-1R agonists mimic the actions of the endogenous hormone GLP-1 in that they stimulate glucose-induced insulin secretion, suppress glucagon secretion and hepatic glucose production and delay gastric emptying. In addition, GLP-1 has been reported to enhance peripheral glucose disposal (very important in diabetes) as well as promote pancreatic beta cell growth and differentiation.[46]

3.2.4. Annexin-A1 Mimetic Peptides

MI remains a major cause of death worldwide and the current therapies based in revascularization of the ischemic tissue (anti-oxidants and calcium channel blockers) have shown insufficient success, novel strategies are needed to treat patients with MI. The main benefits attributed to annexin-A1 peptide mimetics include cardio protection based on their anti-inflammatory effect to preserve myocardial viability after MI but also other inflammation-independent properties that directly protect cardiomyocytes viability and contractile function.[47]

3.3. Peptides used as antimicrobials

Antimicrobial peptides (AMPs) are small peptides essential for the innate immune response of organisms of all branches, presenting activity against a wide range of pathogens, like bacteria, fungi, and viruses. Antimicrobial peptides (AMPs) are found in the innate immune system of a wide range of organism. AMP were considered membrane active peptides regarding their primary activity, but over the years, it was clarified that they can also target different Processes of the pathogen (namely, metabolism and cell division and recruit meant of immune cells. Bacteria present negatively charged membranes, promoting AMP initial electrostatic interaction. Moreover, that number should tend to increase due to advances in the rational design of peptides, minimizing or eliminating cytotoxic effects.

3.4. Peptides used in certain other diseases

Antibodies against TNF alpha can be used in the treatment of psoriasis, rheumatoid arthritis, Crohn disease, and spondilitis. The known peptides proved effective in the treatment are presented in fig. 6.

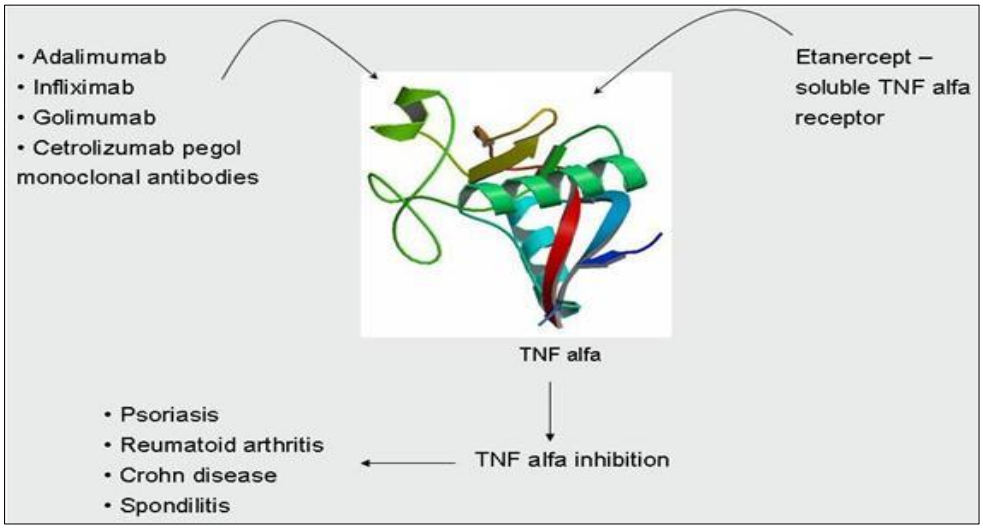

Figure 6 Peptides use in the treatment of psoriasis rheumatoid arthritis, Crohn disease and spondilitis.[4]

3.5. Antibody mimetics

Antibody mimetics are a group of organic compounds that are not structurally related to antibodies but are able to bind antigens and have similar functions to antibodies. Ecallantide is a 60-amino acid polypeptide that specifically binds to kallikrein and inhibits its function. It is applied in the treatment of hereditary angioedema (HAE) and decreases blood-loss in the course of cardiothoracic surgeries.

3.6. Peptides hormones used in Diabetes treatment

The production of peptide hormones (insulin, glucagon) is carried out by protein biotechnological methods. In the body, insulin is produced by the beta cells of the pancreas and its main function is the regulation of blood-sugar level and the

initiation of growth signals. In its absence diabetes develops. This can be type 1 diabetes (congenital or juvenile diabetes) or type 2 diabetes (adult-onset diabetes). According to WHO data in 2000, 2.8% of the whole population suffered from diabetes but according to the prognosis by 2030 as much as 5.5% of the whole population will have been affected. So far, the insulin supplementation has had a great importance and is available for everybody in the form of human recombinant products.[48]

4. Conclusion

The engineered proteins developed in such a form which will behave therapeutically efficient to treat various disorders and diseases are the ultimate thing to achieve in favour of human health. The concept has become popular as well as promising because of several advantages compared to other therapeutics in use. Proteins being the biomolecules inherently are accepted well and do not seem to behave as toxins, so make up the criterion of ideal therapeutic efficacy. The promising use has been studied and proved for diseases such as Cancer, Cardiac diseases, Antimicrobials, Anti diabetics, Hormonal balancing, Vaccines etc. This has clearly enlighted the hopes for their use as effective and non-toxic medicines. Further studies and developmental progress in the concern will surely prove the therapeutic proteins as true 'magic molecules.'

Compliance with ethical standard

Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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