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Bioactive Peptides: An Advanced Version of Antiviral and Immunomodulatory Therapeutics

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Abstract

Bioactive peptides are short chains of amino acids with certain amino acid sequences that have various therapeutic effects. These peptides emerged as new class of therapeutics as they combine special qualities including high binding affinity, superior target specificity, low toxicity, and a relatively tiny mass etc. Some bioactive peptide possess antiviral activity by targeting viral envelop and by inhibiting viral entry into the host cells. They are advantageous as they don't exhibit viral resistance like other conventional antiviral drugs. On the other hand, some bioactive peptides have immunomodulatory effects by reducing the expression of proinflammatory molecules such as IL-6, TNF-α, and COX-2. Bioactive peptides show promise as a potential substitute for or addition to conventional antiviral and immunomodulatory medications.

Keywords: Antiviral; Immunomodulators; Bioactive Peptides; Therapeutics

Abbreviations: HIV: Human Immunodeficiency Virus; LE: Lupus Erythematosus; GIT: Gastrointestinal Tract.

Introduction

Antiviral and immunomodulatory chemicals from different sources have gained attention in the COVID-19 era [1-3]. Bioactive peptides are short chains of amino acids with certain amino acid sequences that have various therapeutic effects. These peptides have crucial physiological regulatory roles in living organisms, such as antibacterial, cholesterol-lowering, antioxidant, immunological modulation, anti-cancer, anti-hypertension, and other physiological actions, in addition to providing energy and vital amino acids [4,5]. These peptides are also serving as the initial line of defense against viral infections and are a component of the innate immune response. The use of peptides as pharmaceuticals began in the 1950s with the discovery of hormones and neurotransmitters, as well as the creation of peptide-based therapies for hormonal therapy [6]. These peptides, both of plant and animal origin, are currently an important area of research because of their use in the food industry, medicine, cosmetics, pharmacology, etc [7]. Bioactive peptides have a number of benefits over small molecules and antibodies in terms of target selectivity and affinities [8,9]. Bioactive peptides can be antiviral peptides (AVPs) that can target several viral replication cycle phases and block them, preventing viral entrance, replication, and assembly. Antiviral peptides come in a variety of types, each with a unique mode of action. Typical types of antimicrobial peptides are defensins, cathelicidins, interferons, thymosins, Mx proteins, Enfuvirtide and peptide aptamers [10,11]. It is crucial to remember that antiviral peptides frequently work against particular viruses or virus families and may have specific targets. While certain AMPs are more general in their antiviral activity, others are more focused. The bioactive

peptides emerged as new class of therapeutics as they combine special qualities including high binding affinity, superior target specificity, low toxicity, and a relatively tiny mass, peptides are a desirable class of compounds for the creation of therapies [12,13].

Bioactive Peptides as Antiviral Therapeutics

Worldwide, viral infections brought on by pathogens such as clinical viruses or newly developing viruses constitute a severe concern. Unfortunately, few treatments are available for a small number of viruses, including the influenza virus, herpes simplex virus, hepatitis virus, and the human immunodeficiency virus (HIV). The AVPs are cutting age therapeutics that can solve such problematic issue. These peptides naturally occur in organisms and protect the organisms from viral infections. For instance, the primary epidermal cells known as keratinocytes serve as both the first site of virus replication and the first line of defense against many different viruses, including arboviruses, enteroviruses, herpes viruses, human papillomaviruses, and vaccinia virus. It has also been observed that these peptides are hardly expressed in healthy skin, but when skin is harmed by outside forces like trauma, inflammation, or infection, their expression rises [11]. The peptide-based antiviral medicines have received approval for the treatment of hepatitis B and C, influenza, and human immunodeficiency virus (HIV) [14].

These cells have the ability to detect molecular patterns associated with viruses during viral replication, which triggers the production of pro-inflammatory cytokines, chemokines, and antimicrobial peptides as part of the innate immune response [15,16]. Further, according to studies done on mice infected with the SARS-CoV, the cyclic peptide RTD-1 (GFCRCLCRRGVCRCICTR) from rhesus macaque leukocytes reduced the disease progression by significantly reducing perivascular infiltration and necrotizing bronchiolitis [17].

It's interesting to note that several AVPs have been shown to have anti-coronavirus (CoV) preventive and therapeutic properties [18]. Additionally a peptide analog called macroporin-M1 (LFRLIKSLIKRLVSAFK) was created through mutation from the original peptide macroporin (LFGLIPSLIGGLVSAFK), which was isolated from the venom of the scorpion Lychas mucronatus, It has been found that this antiviral peptide target viral envelop of coronavirus [18]. Some antiviral peptides function by blocking the entry of viruses into host cells by preventing endosome acidification. In the absence of endosome acidic acidification. The pH-dependent viral fusion protein activation required to start viral-host endosomal membrane fusion did not happen in the absence of endosomal acidification [18]. They inhibit viral replication and infection propagation by preventing viral entrance.

However, anomalous expression of such peptides can hasten viral infections and cause unchecked inflammation in autoimmune disorders including psoriasis and lupus erythematosus (LE) [11].

Advantage of Bioactive Peptides as Antiviral Therapeutics

The interesting fact is that, the antiviral peptides function through a different mechanism than conventional antiviral medications, which makes them less likely to cause the emergence of viral resistance. In the context of newly emerging viral infections and the problem of antiviral resistance, this trait is crucial. Bioactive peptide research is continuous, and researchers are always looking for new peptide candidates for potential therapeutic use. New candidates with potential therapeutic uses are always being discovered through ongoing research into bioactive peptides. They may be used to create novel antiviral therapies as researchers better comprehend their mechanisms and pinpoint specific targets.

Bioactive Peptides as Immunomodulators

Both weak immunity and overactive immunity are problems that can result in a number of diseases. Lack of immunity decreases the body's ability to combat viruses and bacteria that cause infections. On the other hand, very strong anti-inflammatory responses can result in allergies, autoimmune diseases, and hypersensitivity [19]. Bioactive peptides have an impact on all aspects of the immune system, including humoral and cellular immunity, which is discovered while examining their impact on immunocompetent cells. Recent studies have demonstrated that a number of immunomodulatory peptides extracted from the protein hydrolysates of Bombyx mori, Pseudostellaria heterophylla and Cyclina sinensis have good immunomodulatory action in increasing the proliferation of mice spleen lymphocytes and activating macrophage activities [4]. The immunomodulatory effects of bioactive peptides can be proinflammatory and anti-inflammatory [7]. Costa et al. explained the novel peptide which exhibit reduced phospholipase A2 activity responsible for inflammatory cytokine production [20].

The anti-inflammatory peptides are important to treat hypersensitivity and autoimmunity reactions. It has been seen that anti-inflammatory peptides frequently contain hydrophobic (Val, Ile, Pro) and positively charged (His, Arg, Lys) amino acids [21]. The innate immune system components mast cells, dendritic cells, neutrophils, and monocytes are all directly impacted by such peptides [22]. Defensins, for example, are a class of plant peptides that exhibit both immunomodulatory and antibacterial properties, making them intriguing possibilities for the development of

functional foods and feed as well as models for the creation of synthetic peptides [23,7]. Additionally, over the past ten years, there has been a growth in the development of new peptide and peptidomimetic ligands for the CXC chemokine receptor 4 (CXCR4) as therapeutic agents for HIV-1 infection, cancer, and immune system disorders [24].

Source	Peptide sequence	Mechanism	Reference
Whey protein hydrolysate	DQPFFHYN (DN8) and YSPFSSFPR (YR9)	Suppress the release of proinflammatory cytokines	[25]
Yak bone collagen derived	GPAGPSGPAGK, GPAGPSGPAGKDGR etc.	Regulation of NO production and NF-κB signaling pathway and	[26]
sturgeon (Acipenser schrenckii) cartilage	LTGP, LLLE, LLEL and VGPAGPAGP	Reduce the production of NO and IL6	[27]
Ganoderma lucidum	DRVSIYGWG and ALLSISSF	Reduce the expression of proinflammatory molecules such as iNOS, IL-6, TNF-α, and COX-2 in macrophage cells	[28]
Baijiu vinasse	KLPDHPKLPK and VDVPVKVPYS	Inhibit the production of NO and proinflammatory cytokines	[29]

Table 1: display the anti- inflammatory peptides with their source and mechanism of action.

Modified Peptides for Better and Effective Immunomodulation

It has been seen that the natural peptides gone through proteolysis which hampers the bioavailability and stability of such peptides. The bioactive peptides are modified in order to provide better immunomodulation in human body. Extensive research is being done in this area because to the desire for modified peptides with improved stability profiles and pharmacokinetic features [30]. Peptidomimetics are substances that, in terms of their fundamental structure (pharmacophore), imitate a real peptide or protein in three dimensions while yet having the same ability to interact with biological targets and have the same biological effects [30]. These peptidomimetics can help into the treatment of autoimmune disorders as they inhibit the costimulatory effect of T-cell receptor peptide and antigen presenting cells [31].

It would be highly desirable to include immunomodulatory peptides as adjuvants in vaccines, especially in the event of pandemics [7]. However, it's crucial to understand conformational restrictions and B- or T-cell epitopes when designing peptide-based immunomodulating drugs [6]. Immunomodulatory peptides are a complex class of bioactive peptides that encompasses substances with different mechanisms of action. Immunomodulatory peptides could also be used in vaccines as adjuvants which would be extremely desirable, especially in response to pandemics. Thus, immunomodulatory peptides in food of plant origin could be regarded both as valuable supplements of novel functional food preparation and/or as precursors or possible active ingredients for drugs design for treatment variety of conditions arising from impaired function of immune system. Given variety of mechanisms, different tests are required to assess effects of immunomodulatory peptides. Some of those effects show good correlation with in vivo results but others, less so. Certain plant peptides, such as defensins, show both immunomodulatory and antimicrobial effect, which makes them interesting candidates for preparation of functional food and feed, as well as templates for design of synthetic peptides.

Route of Administration of Peptide Drugs

Biotechnology advancements have led to the commercial production of a wide range of peptide medicines. Although the oral administration of drugs provides the benefits of self-administration with a high level of patient compliance but due to inadequate absorption from the digestive system, the majority of these therapeutic peptides are still delivered via parenteral route [32]. For oral delivery of proteins and peptides to be effective, three crucial tasks must be completed: protection of the macromolecules from destruction in the gastrointestinal tract (GIT), penetration over the intestinal barrier, and absorption of the molecules into the systemic circulation [33]. Research is now being done on a number of different strategies, including amino acid backbone modifications, formulation approaches, chemical conjugation of hydrophobic or targeted ligands, use of enzyme inhibitors, mucoadhesive polymers, and absorption enhancers in order to improve oral administration of peptide based drugs [34-37].

Conclusion

In light of newly emerging viral infections and the rising worry over antiviral resistance, bioactive peptides show promise as a potential substitute for or addition to

conventional antiviral and immunomodulatory medications. But for successful clinical application, issues including peptide stability, transport, and safety must be carefully addressed, just like with bioactive peptides. Due to several recent technological developments, peptides are now promising therapeutic possibilities.

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