

# ANTIVIRAL PEPTIDES AS THERAPEUTIC DRUG FOR COVID-19: REVIEW

S. Navya Lakshmi

Department of Microbiology  
School of Bioengineering and Bioscience Lovely Professional University, Phagwara, India.

## ABSTRACT

Covid-19 is life threatening viral disease caused by SARS-COV2 which caused disaster in human life. Initially, non-availability of vaccines and drugs, virus viability remains a major problem for causing diseases in humans. The use of antiviral peptides (AVPs) as a drug are made from natural sources which are highly effective against the corona virus with minimum side effects and cost-effective therapeutic treatment. Antimicrobial peptides (AMPs) are made from immune system which are suitable for development of new peptide based antiviral drug. Design of antiviral peptides and its potential use against corona, antimicrobial peptides, classes of AMPs, synthetic peptides, novel antiviral therapy, biomedical applications and challenges and future prospects are mainly focused and discussed in this paper.

**Keywords:** Covid-19, SARS-Cov-2 Antiviral peptide, antimicrobial peptides, Drug therapy

## INTRODUCTION

Covid-19 epidemic initially caused from market of seafood, Wuhan city, China. (Fakih et al, 2020) [1]. The emergence of recent covid-19 disease clutches the world with concerned and uncertain situation because of high transmission rate from human-to-human infections. Cause of covid-19 is due to SARS-Cov-2 and host surface receptor, human angiotensin-converting enzyme 2 (hACE2). SARS-Cov-2 enters through nose and mouth if particular person is not taking precaution, which effects mainly the lungs, intestines and brain and causes sickness in humans and mortality rates are high with weakened immune system and comorbidity like person with hypertension, diabetes, cancer and obesity (Davidson et al, 2020)[2]. Due to covid-19 pandemic scientists all over the world are working to discover effective drug or vaccine to fight against the virus. There are many drugs available such as remdesivir, chloroquine and hydroxychloroquine can be used for covid-19 but effectiveness is contentious (Maiti et al, 2020)[3]. Single standard, enveloped RNA Corona virus classified into 4 different genera such as  $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ - coronavirus and  $\beta$ -coronavirus include SARS-Cov-2 and SARS-Cov-2 constitute the 7<sup>th</sup> known virus to infect humans which are HKU-NL63, HCoV-229E, HCoVHKU1, HCoV-OC43, SARS-CoV, and (MERS-CoV) Middle East respiratory syndrome coronavirus and showed almost about 1516 variations of nucleotide among many genome annotations and viral resistance occurs due to recurrent adaptive mutations by genome of virus. (Mahmud et al, 2021)[4]. Therefore, developing new antiviral drug or vaccine is the only way to save human life against covid-19. So, development of new antivirals demand increased greatly which may act as an alternative to currently used drugs. Alternative option to solve the issue is make use of Antimicrobial-peptides (AMP) and their biological activities which have different strategies of treatment for bacterial, fungal and viral infections. In recent years peptide-based antiviral had made an interest in use it as a therapeutic-drugs which are accessed from biological, natural and computational sources with having low toxicity and minimum side effects in human (Lei et al, 2019)[5]. These antiviral peptides inhibit the stages by effecting virus life cycle such as their binding, fusion, entry in host cell, replication, transcription, maturation and enzymes of virus. (Heydari et al, Antiviral peptides against Coronaviridae family: A review, 2021)[6]. Antiviral peptides (AVPs) or alternatively called as antimicrobial peptides (AMPs) which have antiviral activities against covid-19 and AVPs are short about 8-40 length of amino acids having polycationic antivirals with wide range of antiviral activities which endeavour prophylactic and effects of therapeutic against covid-19 (Mahendran et al, 2020) [7]. To fight against harmful microbes like virus, AMPs are effective solution and their active molecules are made from many types of microbes as a part of capturing pathogens by innate immune response and database of AMPs have more than 3000 amps along 189 AMPs are having antiviral activities and assessment manifested that lysine, glycine and leucine percentage was more in peptides reported and in contrast with other antimicrobial peptides known only existence of amino acid (lysine) is effective feature for these peptides (Moravej et al, 2018)[8]. In some studies, synthetic antiviral peptides are made for middle east respiratory syndrome coronavirus (MERS-Cov) inhibition and this have capability to fight against covid-19 and these peptides are made on the basis of their HR2 and HR1 region properties of MERS-Cov and these interact with domain of HR1 and stop the formation of fusion core for virus (Zardini et al, 2021)[9]. AMPs convey their work as inducible or constitutively, depending upon what variety of pathogen. AMPs antiviral effect is only against DNA and RNA but not for some nonenveloped viruses and have capability to stop spread of corona virus from cell-to-cell or inhibition of giant cell formation. The aim is to provide happiness among people save them not only from corona virus but also to fight against emerging infection of virus which will increase humans' social welfare (elnagdy et al, 2020)[10].

## POTENTIAL ROLE OF ANTIVIRAL PEPTIDES:

Antiviral peptides which have capability of inhibiting corona virus and are acquired from various approaches that's 1. Natural source like mammals, plants, bacteria 2. Biological source like phage display, bacteria display and 3. Computational source like peptidomimetics, molecular docking (Agarwal et al, 2021)[11]. Various common antiviral drugs like remdesivir, umifenovir and many more are there but due to less efficacy for patients' treatment it can't be used alone. AVP therapy success depend on various factors such as mutation of virus, population of virus genetic diversity, their route of transmission,

replication of virus regulation and persistence of virus in host. Viruses with fast replication and high mutation frequency can control antiviral drugs. So, to avoid this AMPs are favourable as new antiviral drug with new mechanism and they are short about 10-50 amino acids, positively charged and amphipathic oligopeptides which possess structure of high with effective diversity (Maleki et al, 2021)[12] and natural AMPs have a rich origin as new antiviral agents and synthetic peptides copy the natural peptide ability which block censorious steps of virus life cycle. AMPs have ability of viral particle inhibition, host-cell receptors competition, adsorption blocking, stopping interaction in virus and also may vanquish gene expression of virus and provide a solution for resistance of drug because using only single AMP will not be effective but use of 2 or more AMPs or with mixture with conventional treatments to lower the viral escape mutants and to utilise synergistic effects (Falanga et al, 2021)[13]. It also has immunostimulatory effects which increase natural innate immunity and give a novel route to combination therapies having activities of antiviral peptides with various mechanism of action in drugs and also have capability to produce novel AMPs quickly and large therapeutic ratio of AMPs integrating high efficiency and less toxicity in humans (Tonk et al, 2021)[14].

#### ANTIVIRAL PEPTIDE (AVP) ACTION AGAINST CORONA VIRUS:

In the covid-19 pandemic, action of drug is pivotal, and for that peptide-based therapeutics are potent option as a treatment for corona virus infection. The benefits of using peptide based- therapy are: 1. They have potential to stop protein-protein interaction in virus. 2. Can be used as an option for diseases which are tough to target. 3. It can be used as method for the improvement of half-life of peptide and also 4. Require less time to market (Mustafa et al, 2018)[15]. Antimicrobial peptide (AMP) is the part of initial line of defence to the immune system evolved by prokaryotic and eukaryotic organisms which are small gene-encoded, positively charged and are dangerous to bacteria, fungi, protozoans and virus (Pasupuleti et al, 2012)[16] and have different performance such as stopping the inhibition through AMP binding to virus, co-receptors interaction such as CXCR4, cell fusion inhibition through ATPase interference activity of protein, gene expression inhibition, peptide elongation inhibition, and pathway of immune modulatory start up (Sadredinamin et al, 2015)[17]. Their toxicity is because of bilayer of microbes which are rich in lipopolysaccharides (LPS) and lipoteichoic acid (LTA). Peptides build a neutralising epitope which impede the interplay between virus S protein and ACE2 receptor and this epitope are used for generation or for vaccination of an antibody with successful neutralization. The key procedure for antiviral peptide action is categorized into four main class:

1. Peptide which stops the fusion
2. Stops the virus entrance
3. Stops replication and
4. Stops assembly and release of virus (Anand et al, 2021)[18]

Isolation of Antiviral peptide (AVPs) is made from different sources like plants, animals, fishes, insects and also from humans which supposedly exhibit wide antiviral activities in case of viruses such as corona virus by different actions like virus fusion blocking or in hostcell entry, stopping the virus spread by subduing the gene expression, and translation by immune modulatory mechanism inhibition (Sumon et al, 2021)[19]. Formation of virus particle by glycoprotein spike (S), envelope (E), and nucleocapsid (N). Spike is a transmembrane type 1 protein which are created by 2 subunits (S1 and S2) which help in process of entry and S1 subunit possess receptor-binding domain (RBD) which are in accountable for cellular receptor binding while S2 possess fusion peptide (FP), heptad repeat 1 (HR1), heptad repeat 2 (HR2), transmembrane domain (TD) and peptide of cytoplasmic domain (CP), which helps in virus fusion and their entrance in cell (Satarker et al, 2020)[20]. HR1 and HR2 possess 3 parts together that create 6- helix bundle core for fusion and destruction of this core creation can open on to fusion of virus inhibition consequently, stopping the infection. Because of this, Gao et al developed 2 types of AVPs that formed on sequence of HR2 and confront its outcome against MERS-Cov pseudo typed system and P1 peptide exhibit fine inhibitory result. Likewise, method reported by various authors possess that HR2P is able to interact with viral domain HR1 which helps in blocking fusion of virus core formation that's cell-cell fusion stopping test revealed that HRP2 have more efficacy for virus spread inhibition and formation of syncytium (Channappanavar et al, 2015)[21]. Eventually, authors propose that peptide would be as example for analogs plan with increased activity against infection of MERS-Cov and used in patients of clinics and use of peptide- based drug which can be used as adjuvants or as a combination therapy with unlike action of mechanism. Consequently, destroying resistance of drug establishment and making them as a less side effective (Chen et al, 2020)[22]. Ultimately, the novel antiviral drug description gives supplements to the therapies which are existing and give alternative to cure viral disease which cause serious universal problem and decrease the death rate associated with them (Boas et al, 2019)[23].

#### THERAPEUTIC POTENTIAL AND CHALLENGES OF AMPs:

There is a method of action of peptide-based therapeutic against corona virus that's electrostatic attraction caused by cation with phospholipids in anionic form which is there on membrane of microbe and hydrophobicity assist AMPs to include themselves with membrane of virus which cause lysis of virus membrane and allow them to be in soluble form in liquid membrane and aqueous surroundings (Shah et al, 2021)[24]. Peptide-based drug has higher- level choice as therapeutics because of efficacy, specificity, little molecular weight, less toxic, side effects is low, can be accessible synthetically and can be maintained by chemically modified (Madhavan et al, 2021)[25]. But with appeal and many successful invitro result by use of AMPs as antiviral therapy there are also many challenges and drawbacks of using this as a therapy. It is ambiguous that to what range findings of laboratory will translate activity of virus in vivo. The connection of concentration of peptide which are used in invitro experiments psychologically essential concentration which need for in vivo activity that is unspecified for many AMPs. AMPs is less active in assays of invitro which control infections in vivo effectively and less relationship between efficiency

and AMP's dose-dependent obtained from lab experiments and infection by animal models (Giuliani et al, 2011)[26]. Another challenge is AMPs secondary structure will create a problem their production in large scale because it is based on structure and AMPs taken in intravenous form will create degradation of proteolytic, from enzymes in tissues and plasma and short life of AMPs will be there in comparison to small-molecule drugs which can be examined as beneficial in some contexts because of less accumulation in tissues (Shao et al, 2019)[27]. Research to be done further for the relation between AMPs antiviral activity and movement of this activity in in vivo efficiency and should need more AMPs development as a novel class of therapeutics. However, the study has been only explored into experimental animal models and in vitro application and the result will bring the future AMP- based therapeutics which will appear promising (Ahmed et al, 2019)[28].

#### BIOMEDICAL APPLICATIONS OF ANTIVIRAL PEPTIDE:

Corona virus as a pathogenic disease is still a big problem to public health and losses in economy all over the world (Ali et al, 2020)[29]. Antiviral materials having successful synthesis could give novel perception for protection of antiviral development as solutions, potential antiviral agents and drug carriers and drug delivery system of antivirals (Delshadi et al, 2021)[30].

#### **Safety equipment against droplet and aerosol-based entry of virus:**

Material layer of antiviral is needed for safety suits in liquid or in forms of liquid. Nanoparticles of antiviral appeared to be infused mechanically in textiles protective suits or other protective products (Arduzzo et al, 2021)[31].

#### **Potential antiviral agents:**

To avoid spread of resistance of antiviral drug and their mutation, there are some materials of antivirals which are basically biopolymers favourable candidate as antiviral agent, and these are taken from natural sources with low toxic level, low side-effects and supply renewable and biodiversity (Rakowska et al, 2021)[32] and provide complementary and mechanism of overlapping of antiviral action by stopping replication of virus and their synthesis of genome and peptides can be used as synergistic enhancers which help to improve the effect of other antiviral drugs and this effect of synergistic will help to reduce the therapeutic dose and antiviral drug toxicity and also help to reduce antiviral drug resistance induction (Balasubramaniam et al, 2020)[33].

#### **Antiviral Drug carriers:**

There are many systems of carrier that is for antiviral drug which enhance efficacy and specificity for example materials of biodegradable and nanoparticles (Cojocaru et al, 2020)[34].

#### **Drug delivery system of antiviral:**

Many drug delivery systems of antiviral have been there for site-specific targeting of drug which enhance the efficacy of treatment which are specific not only for cells, but also effective for antiviral and antiretroviral therapy (Liang et al, 2020)[35].

Investments by research are achieved by revealing results from translatable scientific investigations into affordable and accessible services of health (Moses et al, 2005)[36].

#### FUTURE PERSPECTIVE OF ANTIVIRAL PEPTIDES:

In finding of most effective antiviral drug against corona virus there is thrilling and impressive discovering that how peptide will act on virus replication and inhibition process. In exploration of most productive antiviral agent for corona virus, there are magnificent and exciting work by peptide which control the virus and the mechanism and stop binding of receptor (Tang et al, 2020)[37]. Also, peptide specific target and selectivity depend on strain of virus. The future implementation peptide- based drugs as novel target is pursuing to be extended (Fosgerau et al, 2015)[38]. Cyclic peptides have presented observation and modification towards surface integration achievement which bridges pharmacology gap of conventional, scaffolds and sequence motives that are putted in cells called cell invading peptides which focuses on innovative peptide-based medicines (Góngora-Benítez et al, 2013)[39]. Poorly defined de-orphanizing target will assist programs of research for novel pairing of membrane-ligand. Another is to improve oral accessibility of peptide application by expanding stabilization of drug in gastrointestinal tract and formation of peptide by increasing CNS absorption by combining with transporting molecules. (Chelliah et al, 2021)[40].

Further, SARS-Cov-2 structure and function will provide extra information about their invasion and virus pathogenesis which will also help to discover antiviral therapies and their design (Sivaraman et al, 2020)[41]. To prevent infection, EK1C4 which is a EK1- derived lipopeptide which used as nasal drop, which rise the medicinal properties and have greater genetic barrier to resistance and can't easily induce drug- resistance mutations and mABs (monoclonal antibodies) which recognise unlike epitopes on SARS-Cov-2 S surface which estimate to neutralize may isolates and escape mutants. Pursuing strengthening SARS-Cov-2 monitoring of S protein will have good significance for novel drug development and defence against covid-19 (Huang et al, 2020)[42].

#### CONCLUSION:

This review on the whole aimed to summarize the antiviral peptides which have appropriate role and gives us relevant information which is used to progress the development of new treatments and suggests that these have efficiency as therapeutic to fight against infectious pathogens like covid-19 (Apostolopoulos et al, 2021)[43] and AVPs having capability to inhibit virus, viral particle inhibition, host-cell receptors competition, adsorption blocking, stopping interaction. Peptide-based drug has higher-level choice as therapeutics because of efficacy, specificity, little molecular weight, less toxic, side effects is low. HR2P is able to interact with viral domain HR1 which helps in blocking fusion of virus core formation and perception for protection of antiviral development as solutions, potential antiviral agents and drug carriers and drug delivery system of antivirals and have many future aspects to be included like cell invading peptides which focuses on innovative peptide-based medicines (C.L et al, 2013)[44], of peptide application by expanding stabilization of drug in gastrointestinal tract and many more. There are not only advantages of peptide-based therapy but also some challenges which are needed to be solved.

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