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REVIEW

ANTIVIRAL EFFECTS OF BACTERIOCIN AGAINST ANIMAL-TO-HUMAN TRANSMITTABLE MUTATED SARS-COV-2: A SYSTEMATIC REVIEW

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KEYWORDS

antimicrobial proteins, antiviral profiling of bacteriocins, antiviral therapeutics, immunomodulation, nanosensor technology, mutated SARS-CoV-2

HIGHLIGHTS

- Identification of bacteriocin sources.
- Classification of bacteriocins.
- Antiviral pathways of bacteriocins.

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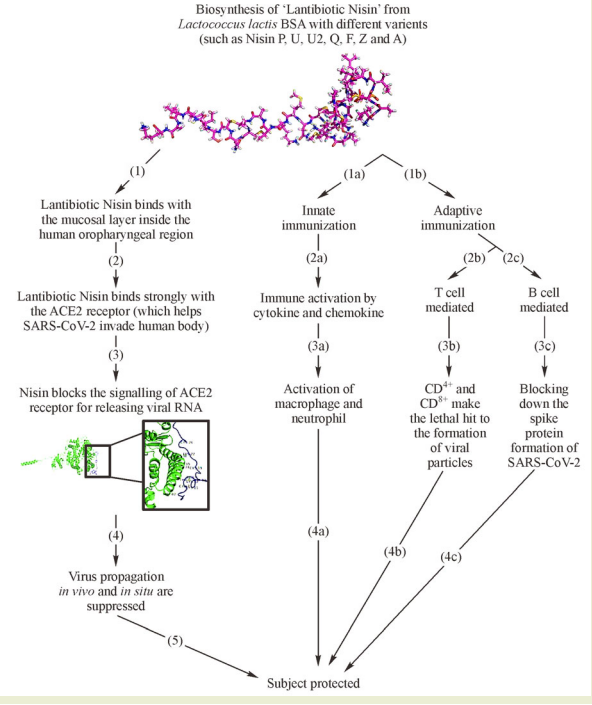
GRAPHICAL ABSTRACT



ABSTRACT

The COVID-19 caused by SARS-CoV-2 has resulted in millions of people being infected and thousands of deaths globally since November 2019. To date, no unique therapeutic agent has been developed to slow the progression of this pandemic. Despite possessing antiviral traits the potential of bacteriocins to combat SARS-CoV-2 infection has not been fully investigated. This review summarizes the mechanisms by which bacteriocins can be manipulated and implemented as effective virus entry blockers with infection suppression potential properties to highly transmissible viruses through comprehensive immune modulations that are potentially effective against COVID-19. These antimicrobial peptides have been suggested as effective antiviral therapeutics and therapeutic supplements to prevent rapid virus transmission. This review also provides a new insight into the cellular and molecular alterations which have made SARS-CoV-2 self-modified with diversified infection patterns. In addition, the possible applications of antimicrobial peptides through both natural and induced mechanisms in infection prevention perspectives on changeable virulence cases are comprehensively analyzed. Specific attention is given to the antiviral mechanisms of the molecules along with their integrative use with synthetic biology and nanosensor technology for rapid detection. Novel bacteriocin based therapeutics with cutting-edge technologies might be potential substitutes for existing time-consuming and expensive approaches to fight this newly emerged global threat.

1 INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has affected 221 countries with about 20.27 million confirmed cases and nearly 2.87 million deaths with 100.6 million active infected cases globally since December 2019[1] and is caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2]. SARS-CoV-2 is a beta coronavirus (βCoV) of the subfamily Coronavirinae in the family Coronaviridae. Coronaviruses (CoVs) possess the largest RNA genomes, ranging from 26 to 32 kb in size, among all RNA virus families[3]. Like other βCoVs, SARS-CoV-2 carries a non-segmented, positive-sense, single-stranded RNA genome of ~ 30 kb, along with an envelope surrounding the nucleocapsid[4]. Instead of having high sequence similarity with a bat SARS-related coronavirus (BatCoV RaTG13) (about 96.2%) and SARS-CoV (about 79.6%)[5], remarkable genetic variation has been found in the SARS-CoV-2 genome resulting in molecular and pathogenic divergence[6]. Clinicians and researchers have been working hard to implement a global vaccination program.

Bacteriocins are antimicrobial peptides (AMPs) synthesized from ribosomes that function against closely- to distantly-related microorganisms[7,8]. Both Gram-positive and Gram-negative bacteria and some archaea have been reported to be capable of producing these peptides[7], especially the probiotic microorganisms including lactic acid bacteria (LABORATORY) that synthesize a wide variety of bacteriocins. These cationic peptides possess a broad spectrum of activities including antibiotic, antiviral, anticancer, and spermicidal activities[9]. Because they have nano-target activities and antimicrobial properties against multidrug-resistant pathogens, even at lower concentrations, these bioactive compounds are currently proposed as substitutes for antibiotic therapies to treat infectious diseases[10,11]. Numerous studies have demonstrated the antiviral traits of bacteriocins against numerous virus diseases[12]. The therapeutic efficacies of these bacteriocins have recently been recognized by researchers but they have previously been used for food preservation[13].

The development of nanotechnology has provided new opportunities to prevent and treat virus diseases. Nanomaterials can reduce the likelihood of the survival of viruses in intracellular environments[14]. Their unique nanometric shapes[15] and large area-to-volume ratios make it possible for them to inactivate viruses by delivering drugs effectively to target sites. In addition,

the invention of synthetic peptide-like biomolecules with the potential to suppress viral threats[16] can be used in treatment of the novel coronavirus. Nanotechnology has already provided us with new antiviral mechanisms along with its biosensing applications. Nano-biosensors are simple, specific and rapid and are promising diagnostic tools for the identification of analytes from viruses helping to eradicate virulence with nanoparticle conjugated antimicrobial peptides[17].

Considering the above issues the objective of this review were to determine the classification and features of bacteriocins obtained from diverse sources and their intended applications after precise manipulation against SARS-CoV-2. Concurrently, the genomic divergence impacts on the COVID-19 transmission chain and altered infection modules were analyzed in detail. Finally, the prospects for antimicrobial bioactive components against coronavirus along with the integration of several state-of-the-art technologies including nanosensor technology are also discussed.

2 BACTERIOCIN RESEARCH LANDMARKS

The extraction and identification of the antimicrobial compounds from differential natural sources commenced in the early nineteenth century. Characterization of bacterial compounds from natural sources with antagonistic effects to syphilis and trypanosomiasis was conducted in 1909 and has been historically known as a 'magic bullet'[18]. Bacteriocins are bioactive peptides documented in several studies in the early 1900s[19], with colicin the first bacteriocin discovered in 1925, with great efficacy against Enterobacteriaceae spp.[20]. The discovery of the first antibiotic, isolated from *Penicillium notatum*, was another landmark in 1928[21], leading to further use and wide investigation of antibiotics over the next few decades as part of bacteriocin research. In the mid 1930s the sulfonamide, p-aminobenzene sulfamide functional against microbes was characterized in France[22]. Despite the important developments in antibiotics from 1941 to 1950[23] the investigation of antimicrobial agents is still underway. Type-A lantibiotics isolated from a bacterial strain of streptococci in the 1960s followe antagonist activity toward human disease-causing pathogens. The lantibiotic salivaricin A is a good example that strongly inhibits Streptococcus pyogenes[24]. The lantibiotic bacteriocin nisin, used as a food preservative approved by FAO/WHO, was isolated from a strain of *Lactococcus lactis* in 1969[19].

Use of bacteriocins specifically in different cancer cell lines was examined in the 1970s as drugs such as pyocin, colicin, pediocin, microcin, and azurin, with azurin found to exert cytostatic and apoptotic effects on cancer cells but no pernicious activity on healthy cells[25]. In 1988, lantibiotics type A and B, isolated from different microbial sources, were found to act against human infectious disease[26] and several researchers isolated two peptide lantibiotics during the late 1990s. Linezolid and daptomycin were registered at the beginning of the twentieth century[27]. In recent decades, discovery of new bacteriocins with novel properties, database development for these peptides, use of bacteriocins for alleviating microbial infections including novel coronavirus treatment, and increasing use in immunoinformatics and vaccinomics, have been emphasized (Fig. 1).

3 BASIC PROPERTIES OF BACTERIOCINS

Bacteriocins exhibit outstanding antimicrobial properties and are secreted from both Gram-positive and Gram-negative microbes and archaea[30]. The AMPs have a biologically active protein moiety attachment to specific cellular receptors, rendering the lethal effects to targeted pathogens by exploiting bactericidal activity. These bioactive peptides are stable over a wide pH range (5–8)[31].

Lantibiotics, also known as Class I bacteriocins, have low molecular weights and are secreted by Gram-positive bacteria. They can withstand high temperatures and extremely acidic environments, and are resistant to certain enzymatic cleavage[32]. Classification of lantibiotics is based on the presence of lanthionine or methyllanthionine bridges as well as dehydrated residues resulting from enzymatic actions[33,34]. These are usually synthesized in their inactive precursor peptide state[35] and are targeted for post-translational modification during their maturation stage leading to possessing modified amino acids in their mature peptide form[33]. They have dual mode of action against susceptible bacteria. Lantibiotics work by becoming an obstacle to the bacterial cell wall, synthesized by binding either to the lipid II or by causing pore formation leading to disruptions in the cell membrane causing death of the bacterial cells[32]. The combination of having antimicrobial properties along with their capability of developing low resistance against pathogens makes them promising candidates for use as therapeutic agents.

Non-lantibiotic bacteriocins are considered as class II bacteriocins. They are small globular-sized, heat stable, positively charged molecules with 30–60 amino acid residues. Post-translational modification is not always needed for efficacy[35]. Their mode of action consists of inhibition of specific enzymes[36] leading to disintegration of the cell wall. Currently,

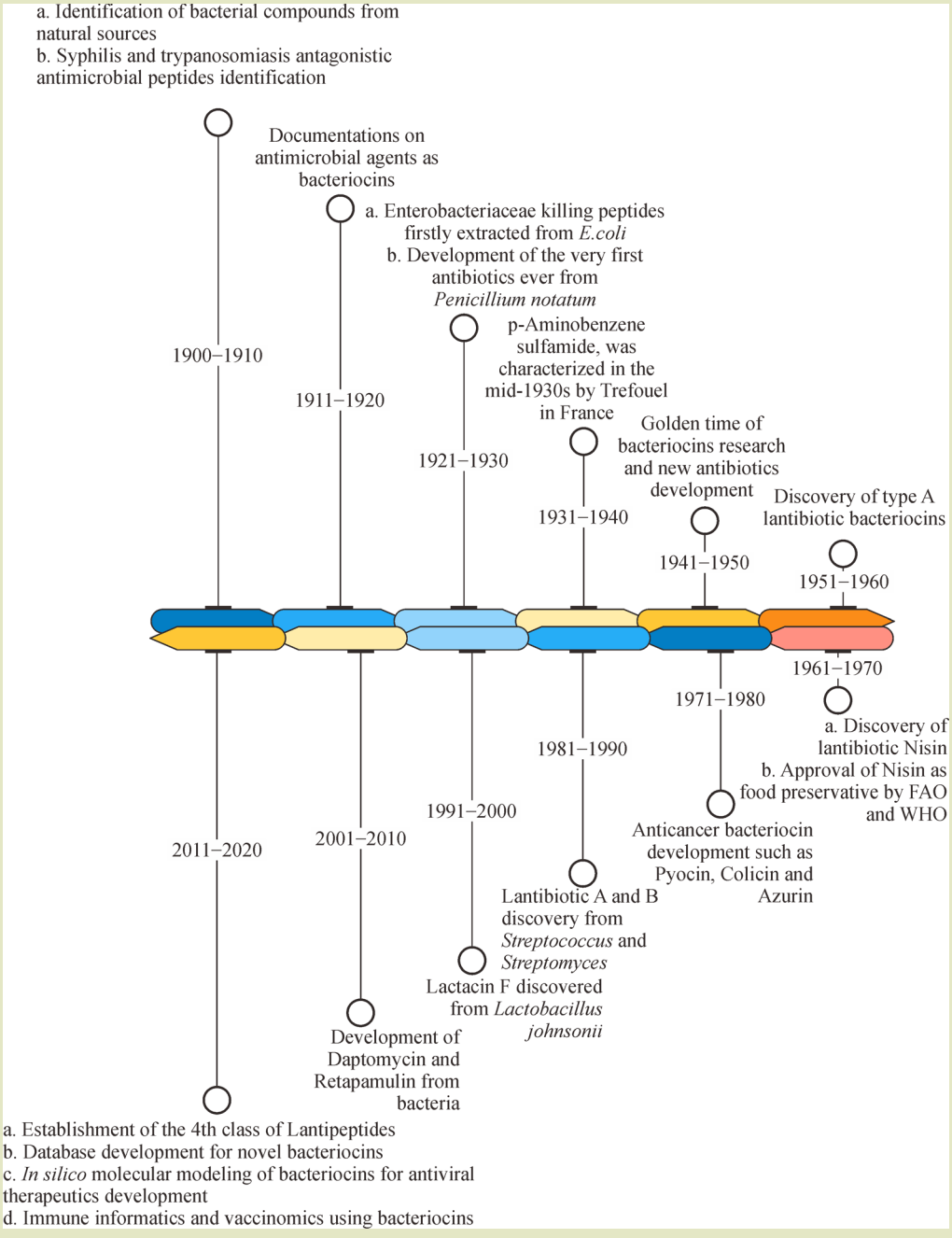


Fig. 1 The landmark discoveries in antimicrobial peptide research over 100 years from the earliest bacterial compound identification in 1909, development of a wide variety of bacteriocins, construction of a bacteriocin database and *in silico* based novel bacteriocin development today[18,20,24,26,28,29]. Scientists are still continuing investigations of the new bacterially secreted proteins with new potential therapeutic targets.

over 50 non-lantibiotics have been isolated and identified from probiotic LABORATORY[37].

Bacteriocins can act on susceptible hosts by triggering bacterial cell lysis and sometimes through bacteriostatic effects[38]. Bacteriocins can even attach to various negatively charged complexes or to lipophilic surfaces of microbial cells[39]. In mammalian cellular systems, the AMPs act as proactive cationic peptides with diversified antagonism[40]. Multiple research approaches have been pursued demonstrating that peptides like nisin induce protective mechanisms in the animal body against pathogenic infections through interactions with the

host immune system[41]. A number of bacteriocins have been reported to affect cell signaling pathways via positive immunization[42].

4 CLASSIFICATION OF BACTERIOCINS

Bacteriocins have efficacy against bacterial[43,44], virus[44] and even fungal[45] infections. The infection mechanism of viruses differs from other pathogens, being organ specific such as in the upper respiratory tract, hepatocytes or genital organs. In fact, influenza A virus, human respiratory syncytial virus and novel coronavirus are able to bind with the respiratory tract and cause mild to severe illness of the infected individuals[46,47]. In addition, exposure to hepatitis B and C viruses can cause disorders of hepatocytes[48].

Bacteriocins are synthesized by both pathogenic and probiotic microbes but bacteriocin production is considered as a probiotic trait for beneficial microbes[49]. LABORATORY are recognized for synthesizing therapeutic bacteriocins for both humans and animals and have been isolated from goat milk[50]. Different bacteriocins have been isolated from microorganisms from diverse sources. Cerein 7 bacteriocin was isolated from *Bacillus cereus*[51] and is considered to be effective against a range of enteric pathogens. Recently cerein 7 from three different *B. cereus* strains was isolated from buffalo milk samples and found to have pronounced immune stimulation properties against induced allergic reactions in birds[52].

Established bacteriocins can be classified into distinct classes based on morphological features, with specified antagonistic potential against the foreign bodies including viruses and bacteria inside the host (Table 1), and this is important in understanding their group-specific antimicrobial properties. In addition, several bacteriocins are classified as antiviral bacteriocins due to their antagonism toward the life-threatening viruses (Table 2). These bacteriocins should be analyzed further to understand their efficacy against SARS-CoV-2 and other influenza-type viruses given the lack of information on the use of bacteriocins against viruses.

5 SARS-COV-2 TRANSMISSION INTERFACE BETWEEN HUMANS AND ANIMALS

The transmission of viruses from species to species is a natural process. Humans can come into contact with the various animals as food or in many other ways[76]. Normally the successful mutations of viruses for the transmission from animals to humans occurs at a frequency of one in 100 years[77]. Virus transmission from one species to another is enabled by entry receptors for the viruses in the new host's cytoplasmic membranes[78]. Evolutionary theory suggests that minimal spontaneous selection mechanisms are responsible for infection efficiency, minimal lethality and, occasionally, contagiousness efficiency of the viruses[79].

Most pandemic causing viruses are reported to have multiple mutations in their genome, which can generate cross-species infections[80]. The four known types of coronavirus are HCOV-OC43, HCOV-NL63, HCOV-HKU1 and HCOV-229F[81]. These can infect humans but this is accompanied only by a number of mild symptoms[82]. The ages of these human-infectious coronaviruses are > 150 years[83]. The SARS-CoV-2 is the fifth member of this group and is more organized in infecting the human communities than the other four[86] (Fig. 2).

6 HISTOPATHOLOGICAL STATUS OF SARS-COV-2 AS COMPARED TO SELECTIVE SIMILAR VIRUS TYPES

Antibody-dependent enhancement (ADE) is thought to be responsible for the acute clinical symptoms associated with COVID-19. However, ADE is not liable for the recognition and clearance of the virus, rather it forms virus-specific antibodies which can expedite the uptake and stimulate the replication of the virus[87]. Additionally, this mechanism avoids innate immune sensors or pattern recognition receptors[88]. Studies have been conducted on the ADE mechanisms which are found in Flaviviruses and they are responsible for 90% of patients who suffer from hemorrhagic fever and DENV shock syndrome related to dengue virus[89]. Unwanted histopathological changes at virus infection sites were observed among the experimental animals when the SARS-CoV-1 vaccine trials commenced and these changes might have occurred due to filtration of lymphocytes, monocytes and eosinophils[90]. Eosinophils can stimulate T-helper type 2 and 17 immune responses, which have an important role in the increase in viral expression of the SARS nucleocapsid protein[91]. A strong association between T-helper type 17 responses and IL-6 is overexpressed in patients with COVID-19 and these patients experience a cytokine storm along with the stimulation of IL-8[92]. In a recent pandemic the D480A/G had a tendency to escape from neutralizing antibody 80R which can form the D480 mutation. Most researchers discern the trimeric spike protein which mediates host cell binding and entry. This is a major factor in the neutralization of antibodies[93]. Genetic modifications, particularly mutation and

Table 1 Brief classification of the bacteriocins collected from both the Gram-positive and Gram-negative bacterial strains whose efficacies for being used as therapeutic against diseases have been studied

Classes	Names of the bacteriocins	Producing microorganisms	Antagonistic activity toward	References
		Extracted from Gram-positive bacteria[a]		
Class I-lantibiotics	Nisin	*Lactococcus lactis*	*Lactococcus*, *Streptococcus*, *Staphylococcus*, *Listeria*, and *Mycobacterium*	[51,53]
	Subtilin and subtilosin	*Bacillus subtilus*	*Staphylococcus simulans* and *Bacillus subtilis*	[54]
	Pep5	*Stapgylococcus epidermidis*	*Staphylococcus* spp.	[55]
	Mutacin B-Ny266	*Staphylococcus epidermidis*	*Neisseria spp.* and *H. pylori*	[55]
	Mersacidin	*Bacillus* spp.	Methicillin-resistant *S. aureus*	[53]
	Enterocins	*Enterococcus faecalis*	*Clostridium botulism*, *Bacillus cereus* and *Geobacillus stearothermophilus*	[55]
Class II-non-lantibiotics[Ψ]	Pediocin PA1	*Pediococcus acidilactici* UL5	*Listeria ivanovii*	[56,57]
	Leucocin-A	*Leuconostoc gelidum* UAL-187	*Listeria monocytogenes*, *Enterococcus faecalis*, and lactic acid bacteria	[58]
	Thermophilin 13	*Streptococcus thermophilus*	*S. thermophilus*, *C. botulinum*, *L. monocytogenes*, and *B. cereus*	[53]
	Lactococcin G	*Enterococcus faecium*	LABORATORY (*), *Clostridium* spp.	[53]
	Uberolysin	*Streptococcus uberis* strain 42	*Streptococci* (with the exception of *Streptococcus rattus* and *S. mutans*), *Listeria* spp., *Enterococci* spp. and *Staphylococci* spp.	[59]
	Enterocin B	*Enterococcus faecium* T136	*Influenza virus*	[60]
Class III bacteriocin	Lysostaphin	*Staphylococcus simulans*	*Staphylococcus aureus*, *Staphylococcus epidermidis*	[61]
	Zoocin A	*Streptococcus equi*	*Staphylococcus mutans*, *Staphylococcus sobrinus*, *Staphylococcus cricetus*	[62]
	Millericin B	*Streptococcus milleri*	*Streptococcus pneumonia*, *Bacillus anthracis*, *Corneybacterium diphtheriae*	[63]
	Enterolysin A	*Enterococcus faecalis*	*Enterococcus faecalis*, *Pediococcus acidilactici*, *Lactococcus lactis*	[64]
	Propionicin SM1	*Propionibacterium jensenii*	*Propionibacterium jensenii*	[65]
	Dysgalacticin	*Streptococcus dysgalactiae*	*Streptococcus pyogenes*	[35]
	Albusin B	*Ruminococcus albus*	*Ruminococcus flavefaciens*	[66]
Class IV bacteriocin	Enterocin AS-48	*Enterococcus faecalis*	*Listeria monocytogenes*, *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*	[35]
	Gassericin A	*Lactobacillus gasseri*	*Alicyclobacillus acidoterrestris*, *Bacillus* spp., *Paenibacillus* spp., *Geobacillus stearothermophilus*	[67]
	Reutericin 6	*Lactobacillus reuteri*	*Lactobacillus acidophilus*, *Lactobacillus delbrueckii*, *Lactobacillus delbrueckii*	[68]
	Circularin A	*Clostridium beijerinckii*	*Clostridium tyrobutyricum*	[67]
	Uberolysin	*Streptococcus uberis*	*Streptococcus parauberis*	[59]
		Extracted from Gram-negative bacteria[b]		
Pathogenic source of bacteriocins	Colicins	*E. coli*	*E. coli φ*	[69]
	Microcins	*E. coli*	*Enterobacteriaceae*	[20]

Note: [Ψ]Non-lantibiotic bacteriocins are more thermostable and cationic in nature than the lantibiotics. [a]Gram-positive microorganisms have been considered as the prime sources of antimicrobial peptides (metabolites) having therapeutic potential. [b]Gram-negative pathogens synthesize non-lantibiotic bacteriocins. *LABORATORY (lactic acid bacteria) are novel probiotic supplements and act as major sources of bacteriocin.

Table 2 Selective established bacteriocins dedicated for antiviral activity against the life threatening viruses

S.N.	Name of the bacteriocin	Classification	Bacteria name	Antagonist activity to the virus**	Reference
01	Enterocin CRL35	Class IIa	*Enterococcus faecium CRL35*	Herpes simplex (HSV) type 1 and 2	[70]
02	Enterocin AAR-71	Class IIa	*Enterococcus faecalis AAR-71*	Coliphage HSA	[71]
03	Enterocin AAR-74	Class IIa	*Enterococcus faecalis AAR-74*	Coliphage HSA	[71]
04	Enterocin NKR-5-3C	Class IIa	*Enterococcus faecium NKR-5-3*	HSV-1	[12]
05	Labyrinthopeptin A1	Class IIa	*Actinomadura namibiensis DSM 6313*	HIV-1 and HSV-1	[72]
06	Subtilosine	Class IIa	*Bacillus amyloliquefaciens*	HSV-1	[73]
07	Erwiniocin NA4	Class IIa	*Erwinia carotovora NA4*	Coliphage HSA	[71]
08	Enterocin ST5Ha	Class IIa	*Enterococcus faecium ST5Ha*	HSV-1	[74]
09	Enterocin ST4V	Class IIa	*Enterococcus mundtii ST4V*	HSV-1 and HSV-2	[74]
10	Enterocin CRL35	Class IIa	*Enterococcus mundtii CRL35*	HSV-1 and HSV-2	[74]

Note: **The therapeutics used for HSV can also be used against SARS-CoV-2 as reported recent most established research works[75].

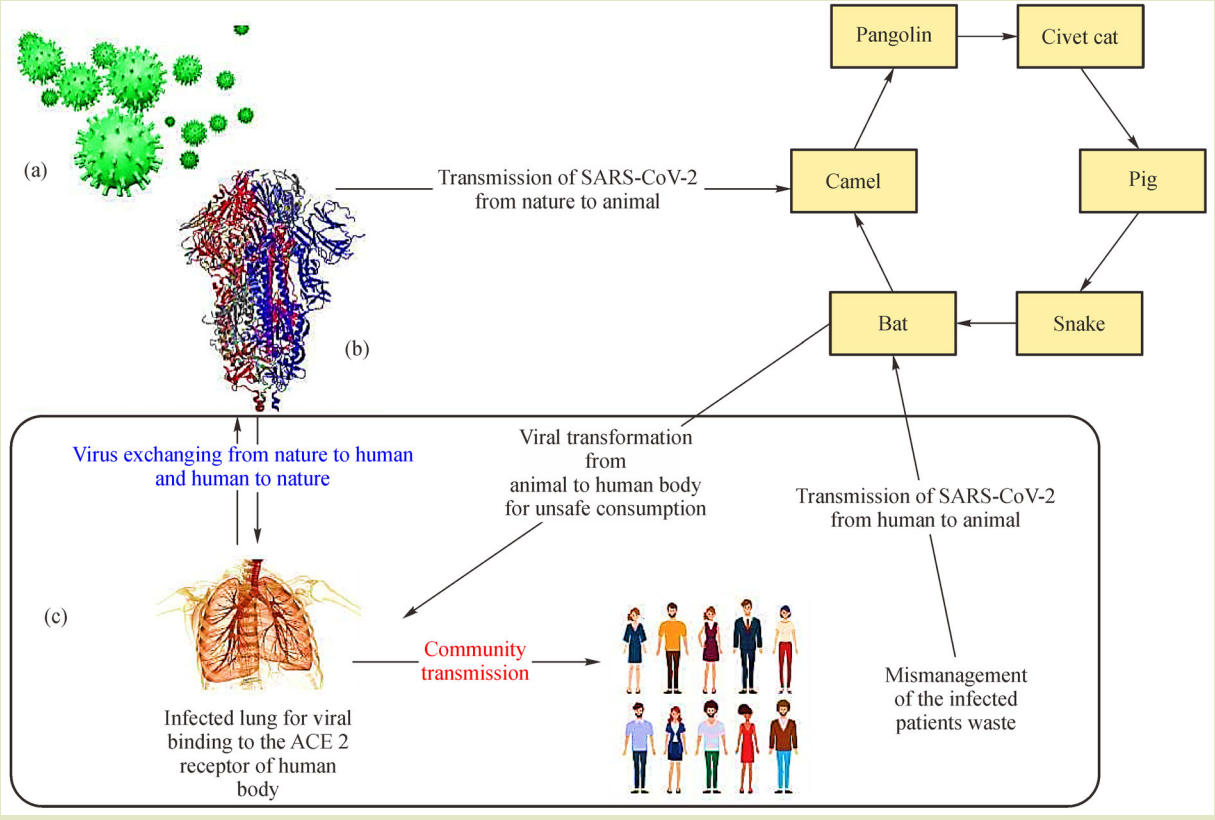


Fig. 2 (a) Diagrammatic representation of the SARS-CoV-2 virus 3D view, (b) the spike protein of the virus, (c) the interface of the points from where the virus is exchanged from nature to humans, humans to nature, animals to humans, and humans to animals[84,85].

recombination, are common events occurring among RNA viruses due to having an error-prone RNA-dependent RNA polymerase (RDRP)[94]. Both SARS-CoV-1 and SARS-CoV-2 spike proteins use the human angiotensin-converting enzyme 2 (hACE2) receptor for attachment and entry[95]. The hACE2 receptor is found mainly on epithelia of the lungs, suggesting a likely cause of respiratory illness and lung damage in advanced stages of the infection. No amino acid substitutions have been

reported in SARS-CoV spike protein[96]. N501T[97], V367F[98] and V483A[99] mutations in the receptor binding determining region (RBDR) result in the enhanced ACE2 receptor binding with SARS-CoV-2 spike protein making the human body more prone to infection. However, expression of this receptor in many other tissues is also reported[100].

In contrast to SARS-CoV-1, the RBD in the S protein of SARS-CoV-2 exerts stronger binding affinity to the hACE2 receptor macromolecule. Consequently, cell entry occurs more effectively/efficiently[98,101]. Different lines of research have explained the high hACE2 receptor binding affinity through genomic and proteomic analysis[97,102]. In addition, these modifications give rise to the antigenicity of SARS-CoV-2. The genome organization of the SARS-CoV-2 is illustrated for further clarification (Fig. 3).

Mutations and recombination have been studied to correlate with genome variability, pathogenicity, severity, transmission ability and, most importantly, evolvability of the SARS-CoV-2[103–105]. In SARS-CoV-1, only a single amino acid is mutated inside the Spike D614/G protein. This single amino acid change was constant among infected individuals and was the predominant variant in the 2003–2004 SARS-CoV-1 epidemic[106].

7 INTENDED IMMUNE SIMULATING ACTIVITY OF BACTERIOCINS AGAINST SARS-COV-2

Bacteriocins can induce innate immune response through the stimulation of immune cells[107] which can generate phagocytosis reactions. Opsonins are the main precursor molecules that can induce phagocytosis acting as effective bridges between innate and adaptive immunization[108] at the time of any alienating foreign particle such as when viruses coexist with other protective cells. Bacteria-secreted molecules interfere with virus entry by blocking the cell surface receptor (e.g., hACE2 receptor for stopping SARS-CoV-2) of the host, consequently reducing the virus load in the body and/or rupturing the virus at an early stage[109]. Bacteriocins, in particular the lantibiotics, have immune modulatory properties and previous investigation reveals that the immune modulation mechanisms of nisin subunits are analogous to those of the human cationic peptides, including LL-37 and defensins[110]. These antimicrobial peptides affect the innate immune system through the induction of IL-8, MCP-1 and Gro-α secretion and suppression of bacterial LPS-induced TNF-α synthesis in human peripheral blood mononuclear cells (PBMCs)[110] (Fig. 4).

The role of lantibiotic nisin in the alteration of innate immune responses was further assessed in human polymorphonuclear neutrophils *in vitro*[116]. Neutrophils kill pathogens through neutrophil extracellular trap formation[117,118] and phagocytosis accompanied by oxidative burst[119]. Neutrophil extracellular traps (NETs) are a form of innate immune response which limits the spread of infection and its formation is usually triggered by phorbol myristate acetate PMA and IL-8 cytokine in response to bacterial LPS[117]. Oral administration of nisin-containing food resulted in the elevation of both $CD4^+$ and $CD8^+$ T-lymphocytes and the depletion of B cells in mice[118]. AMP-producing probiotics also modulate the immune response of different immune cells through stimulation of both anti-inflammatory and pro-inflammatory cytokines[111]. The genetic loci containing genes for bacteriocin biosynthesis, identified in Lactobacillus plantarum, have been found to modulate the cytokine response of dendritic cells and human PBMCs and subsequent T-lymphocyte induction[120–122].

Bacteriocins, including subtilosin and enterocin CRL35 and ST4V were found to manifest antiviral action against HSV-1 and HSV-2 grown on the Vero cell-line[70,74,123]. Both *in vivo* and *in vitro* experiments showed the antiviral activity of staphylococcin 188 against influenza and Newcastle disease virus. SARS-CoV-2 is an influenza-like virus and bacteriocins can provide a similar type of infection-prevention mechanism as reported in other influenza-type viruses[124]. The anti-HIV activity of Laby A1 peptide has been demonstrated in numerous studies. Laboratory A1 has consistent anti-HIV-1 activity against nine distinct HIV-1 clinical isolates. This carbocyclic lantibiotic

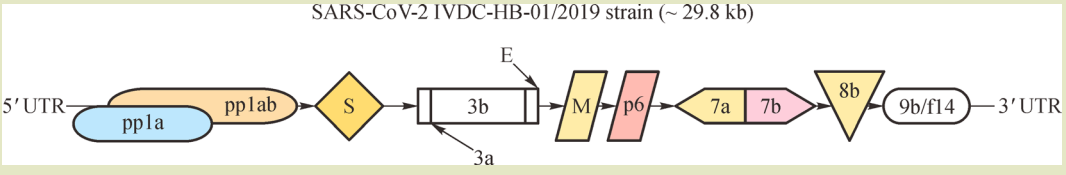


Fig. 3 Illustration of the genomic orientation of SARS-CoV-2 (~ 29.8 kb) retrieved from the 2019 outbreak and the encoded proteins pp1ab and pp1a for the IVDC-HB-01/2019 (HB01) strain[96].

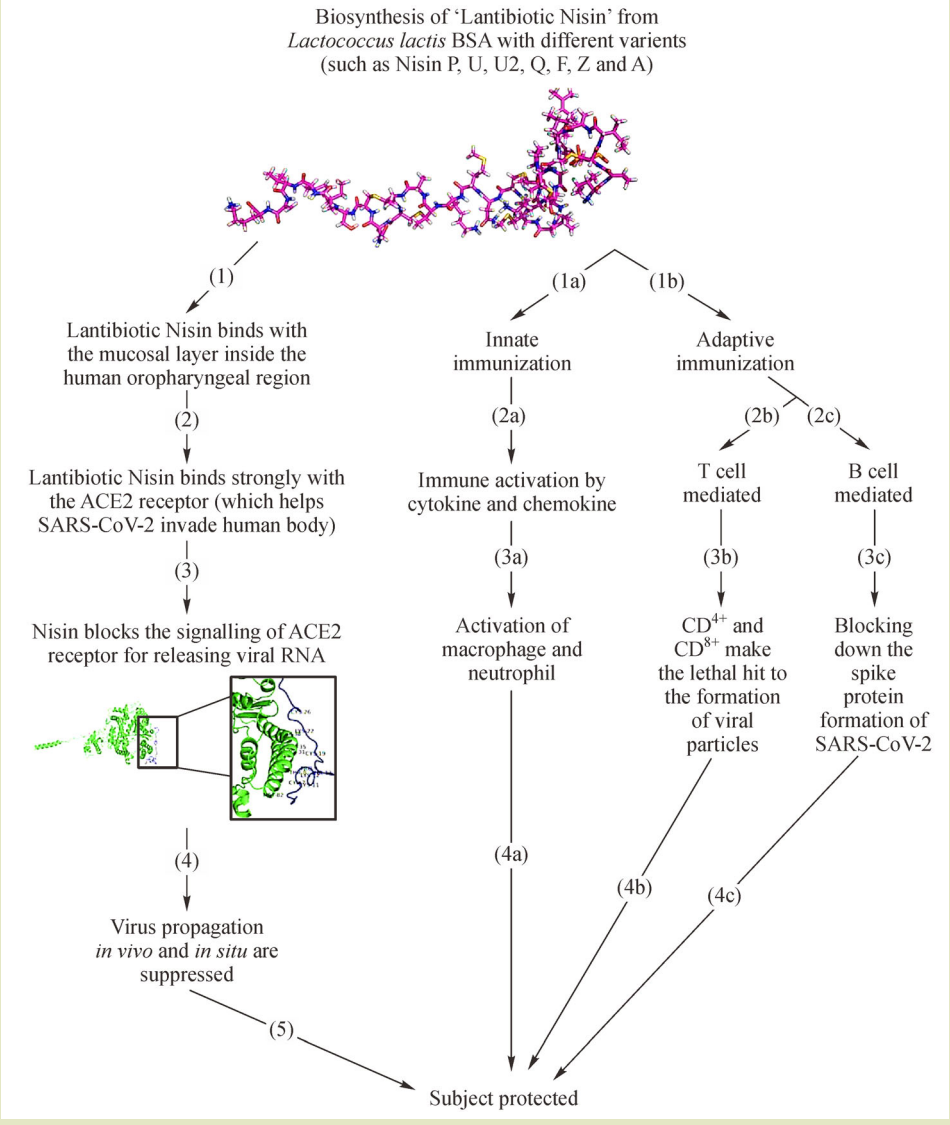


Fig. 4 Bacteriocin mediated immunization pathway with nisin as an effective candidate of the lantibiotic bacteriocins. At the first step the bioactive compound tends to bind with the mucosal layer of the individual and strongly blocks the ACE2 receptors for inhibiting the virus propagation within the organism. This post transcriptional modified compound is directly interconnected to the innate and adaptive immunity. Innate immune cells such as-neutrophils and macrophages are activated by this peptide and encounter the pathogenic entities to eliminate them from the body. Following activation of the innate immune cells like macrophages and neutrophils, pathogenic entities are eliminated from the body by encountering these cells. In contrast, adaptive immunity activates immune fighters such as T and B cells. T cells involve the lethal hit to pathogenic traits via the $CD4^+/CD8^+$ T cell but at the last step B cells directly block the viral spike protein. Of note, following these mechanisms, the entry and propagation of novel coronavirus within the human body can be blocked, as suggested in the literature[110–115].

further blocks intracellular virus transmission between persistent HIV-infected T-lymphocytes and uninfected $CD4^+$ T-lymphocytes[72].

Several strains of Laboratories capable of producing antimicrobial peptides function against influenza virus infection by multiple mechanisms such as activation of Th1- mediated immune response, stimulation of pro-inflammatory cytokine secretion and induction of B cell driven antibody production[12]. The rejuvenation of innate and adaptive immune responses against influenza-like viruses including SARS-CoV-2 can be mediated by the oral delivery of Lactobacillus gasseri, a prominent candidate for production of antimicrobial peptides[125]. A strain of Lactobacillus rhamnuosus conferred immunity against RSV (respiratory syncytial virus) infection by triggering the release of IFN-γ and other ILs[126]. Laby A1 and

A2 lantibiotics can inhibit respiratory syncytial virus cell entry through interaction with the phosphatidylethanolamine (PE) lipid moiety of the virus capsid which is similar in SARS-CoV-2 suppression. The anti-RSV activity of these peptides was documented both in human lung cells and their carcinoma-derived counterparts *in vitro* and *in vivo*[127,128]. Recently the virolytic effect of Laby A1/A2 was observed against an array of enveloped viruses[129] including SARS-CoV-2. The virolysis process can also be mediated through binding of these lanthipeptides with viral PE with no cytotoxicity to host cells observed. Bacteriocins possess antiviral activity along with other miscellaneous activities including antibiotic, anticancer and spermicidal activities[9]. Bacteriocins are active toward the diverse respiratory tract infection prevention caused by influenza virus, human rhinovirus, respiratory syncytial virus, SARS-CoV-2 and SARS-CoV-1[130,131]. Some reports indicate that bacteriocins from supernatants of lactic acid bacteria have antagonistic activity toward the novel coronavirus-type influenza viruses including influenza viruses A (strain H7N7)[132]. In addition, the antimicrobial peptide staphylococcin 188 can eliminate respiratory infection in humans[12]. However, probiotic bacterial strains produce some potential antibiotic peptides (mainly bacteriocins) that may prevent the infection of human rhinovirus and/or respiratory syncytial virus[133]. Also, some potential bacteriocins isolated from probiotics have significant activity toward SARS-CoV-2 infection[128]. Conversely, Plantaricin BN, Plantaricin JLA-9, Plantaricin W, and Plantaricin D are active against the various receptors of SARS-CoV-2 along with receptors in humans with such antiviral agents showing better results during *in silico* simulations[134].

8 PROSPECTS OF SARS-COV-2 RESEARCH WITH ANTIMICROBIAL MACROMOLECULES

In January 2020, China provided the genetic sequence of the SARS-CoV-2 in a publicly-available database enabling global development of therapeutic drugs and vaccines. Two months later a biotechnology company (Moderna Inc., Cambridge, MA) developed a specific and unique candidate vaccine, a lipid nanoparticle encapsulated nucleoside-mRNA vaccine[135]. The mRNA vaccine stimulates the immune response via the spike glycoprotein which facilitates the entry of the virus particles into the host cells[136]. Moderna completed phase 1 clinical trials on humans in mid-March and released their results indicating success in mid-May 2020. Infrequent adverse effects were mild to moderate and the vaccine brought about robust antibody responses against the spike proteins and the presence of the antibodies has been confirmed[137]. After overcoming hurdles with ADE and cellular immunopathology concerns, the candidate vaccine was approved for phase 3 trials in early June with 30,000 participants in the United States[138].

Enhancement of the efficacy of the COVID-19 vaccine is required to develop a novel treatment system for COVID-19 patients worldwide. Any effective vaccine must have the ability to enhance the T cell response *in vivo* to develop long-term protection. Here, the peptide vaccines are considered as an alternative to standard vaccines that aim to resolve the problems of potential side effects of vaccines due to heterogeneous multicomponent preparation vaccinations. *In vitro* synthesized peptides of 20–30 amino acids, considered to be highly immunogenic and activating the desired immune response, are based on peptide vaccines. Numerous preclinical and clinical studies generally demonstrate easy synthesis with low cost, improved stability and relative safety[139]. As the situation deteriorated during the SARS-CoV-2 pandemic the need to design an effective SARS-CoV-2 peptide vaccine component grew and several pharmaceutical companies developed some SARS-CoV-2 peptide vaccines[140]. In a toxoid vaccine made from bacteriocins which is harmless but provides an immune reaction to any type of infectious viruses, usually exotoxins are secreted by post pathogenic infections from the pathogens as cellular metabolites. The toxin invades the bloodstream and is subsequently responsible for the disease symptoms. The protein-based toxin is rendered harmless and the toxoid is adsorbed to aluminum or calcium salts which serve as adjuvants, in order to trigger and improve the immune response[141].

A DNA vaccine has provided a promising gene therapy application by transfecting the cells of an immunized species with a particular antigen-coding DNA sequence[142]. A ground-breaking approach to the induction of humoral and cell-mediated antigen-specific immune response in systemic and mucosal compartments is defined by DNA vaccines. Vaccines consist of DNA-encoding plasmid antigens that are expressed in host cells, including post-translational modifications unique to the species[143]. In addition, the technology of recombinant DNA vaccines includes injecting an antigen (such as a bacterial surface protein) encoding DNA that induces an immune response into both bacterial and mammalian cells, expressing the antigen in these cells. In the proteasome of the transduced cell the antigens are gradually broken down and present in the form of MHC class I molecules as externalized peptides, thus increasing the response of $CD8^+$ T cells[144]. However, the recombinant protein vaccines create a range of issues related to vaccines based on purified macromolecules that need to be prevented, such as the possibility of co-purification of undesired contaminants or

reversal of toxoids to their toxic forms if, for example, diphtheria or tetanus toxoid vaccines were being considered[145].

The complementary strategy of the genome-based approach is used to produce proteomic vaccines in which both immune informatic and vaccinomic strategies are involved[146]. Much research is needed to develop an effective proteomic vaccine against the SARS-CoV-2[147]. In addition, synthetic biology vaccine technology typically involves the use of computer-assisted biological engineering to develop and construct new biological components, equipment and structures that do not exist in nature, and reconstruction of existing biological systems for the purpose of conducting activities against infectious viruses[148,149] including SARS-CoV-2.

Recently, understanding the immune responses that can be modulated by nanoparticles to attain desirable effects has been an important issue in vaccine formulations based on nanoparticles. Nanoparticles can operate both as a delivery system to enhance antigen processing and as an immune stimulatory adjuvant to induce and heighten protective immunity[150,151]. Also, a subunit vaccine is a vaccine that presents one or more antigens to the immune system without introducing pathogen particles, whole or otherwise. The Vi capsular polysaccharide vaccine is a subunit vaccine against typhoid caused by the Typhi serotype of *Salmonella enterica*[152].

Synthetic biology and bioengineering interventions have already provided hyperactive bio-compounds with remarkable peptide stability[153] and hyperactivity such as pyocin S-35, lactococcin G and microcin V[16]. Integration of nanotechnology has enhanced the diagnosis of and research on COVID-19 in ways not possible in the past. To optimize drug administration methods for SARS-CoV-2, nanotechnology has attracted attention globally. Nanomaterials having nanometric shape[15] and large surface area-to-volume ratios make it possible to deliver drugs across impermeable barriers[154]. Oseltamivir is the most widely used antiviral drug for H1N1 influenza virus types A and B, which is also suggested as being potentially effective against novel coronaviruses. Oseltamivir OTV has been found to work more efficiently against H1N1 when this drug is delivered associated with SeNPs (selenium NPs)[155]. Functionalized gold NPs (14 nm) blocked influenza A virus infection but 2 nm AuNPs (gold NPs) did not provide any significant benefit[156]. In the 2009 influenza A virus, copper iodide NPs were used to inactivate virus proteins (e.g., hemagglutinin and neuraminidase) through reactive oxygen species[157]. As SARS-CoV-2 is an influenza-type virus, a highly precise diagnosis strategy will be effective in its early detection and its potential treatment as with other influenza viruses[158].

AgNPs (silver NPs) coated with polyvinylpyrrolidone (PVP), bovine serum albumin and carbon can hinder the interaction of HIV-1 (human immunodeficiency viruses) with living cells by binding to the gp120 glycoproteins of the virus envelope[159]. Similarly, the ability to prevent HIV-1 infection of cells can be improved by the addition of 30–50 nm PVP coated AgNP neutralizing antibodies. AgNPs work against the hepatitis B virus by inhibiting the replication of viral DNA.

Carbon quantum dots (CQDs), derived from hydrothermal carbonization of ethylenediamine or citric acid as carbon precursor and further modified with boronic acid ligands resulting in the first-generation nanostructure, have demonstrated potential to inactivate HCoV (human coronavirus)[160]. CQDs derived from 4-aminophenyl boronic acid are the second generation of anti-HCoV nano-materials. CQDs at 10 nm have excellent dispersion in water and may be an advance in nanomedicine. According to the data cited above it is possible that the current SARS-CoV-2 pandemic can be brought under control by deployment of nanotechnology approaches.

NPs are in great demand as drugs for treatment purposes and also for any type of critical diagnosis. The detection of viruses using nano-materials was first attempted with AuNPs combined with silver staining for the diagnosis of human papillomavirus in cervical carcinoma cells[161]. AuNPs have been used in advanced SARS diagnosis focusing on rapid and specific molecular detection through two main assays: a colorimetric assay for pp1ab (polyprotein 1ab) gene detection and an electrochemical assay for nucleocapsid protein gene detection. In the colorimetric assay the presence of target SARS nucleic acids can be seen from a change in color of the solution from red to blue. This change arises from the aggregation of AuNPs with the target particles. Electrode conductivity and the surface available for detection probe immobilization can be enhanced by using AuNPs in the electrochemical assay[162]. In addition, a nanobiosensor which has three main modules, namely a transducer, a receptor and a detector (Fig. 5), based on the principle of capturing of target and transformation of the responses to signals, has become a new and promising tool for SARS-CoV-2 virus detection[17].

An electroluminescence sensor to identify the HIV-1 gene was promoted by scientists and it has been demonstrated to have useful specificity[163]. A graphene-based nanosensor was developed to detect Zika virus antigens in human serum down to 450 pmol·L^{-1}[164]. The concepts of quantum dot-based nanosensor development can be considered one of most promising future methods for SARS-CoV-2 detection, bypassing the time-consuming and comparatively costlier RT-PCR techniques.

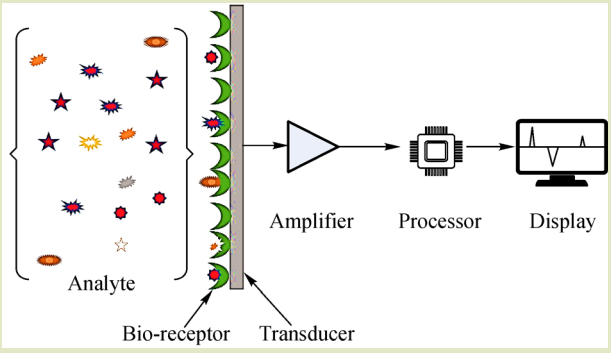


Fig. 5 The interaction of the analytes with the bio-receptor produces a physicochemical signal. This signal is then processed to an electrical signal to be measured by the transducer. The variation in signals such as electric potential, current, conductance, impedance, intensity and mass, temperature and viscosity are monitored to quantify the presence of bio-agents. The measured information is processed to demonstrate the results.

9 INTEGRATION OF TRADITIONAL CHINESE MEDICINE IN SARS-COV-2 RESEARCH WITH VACCINES AND BACTERIOCINS

Traditional Chinese medicine (TCM) has been used of thousands of years as a means of preventing and combating epidemic diseases and is known to provide important benefits. It integrates thousands of years of experience from the constantly emerging infectious disease that have occurred since ancient times in China[165]. TCM is one of three major traditional medicines globally that holds a vital position in the Chinese national medical system and enjoys global popularity[166]. TCM showed surprising results in the prevention and treatment of SAR-CoV-1 in 2003. Due to the great sequence and infectivity homology between the SARS-CoV-1 and SARS-CoV-2, it is expected that the strategies used for SARS-CoV-1 will provide precedence for the prevention and treatment of SARS-CoV-2[167].

TCM theory states that a body will not succumb to a disease even if exposed to the pathogenic factors as long as the body is healthy and well-endowed with sufficient and balanced zhen qi and yin and yang. When it comes to the treatment of a disease, TMC treatment plans take a different route to recovery by keeping the prime focus on driving away the exogenous pathogen with the restoration of the self-healing of the body rather than directly eliminating the pathogen. This method, unlike modern medicines, keeps the host cells from any harm[168]. Another theory upheld by TCM is the prevention of the disease, i.e., preventing the disease to fully establish itself in the body and also preventing the progression of the disease from mild to severe after it has occurred. Decades of experience show that TCM has greater potential in preventing and controlling epidemic diseases due to its treatment based on syndrome differentiation and also on clinical manifestations of individual patients[169].

The National Health Commissions of China has issued seven editions of diagnosis and treatment protocols for COVID-19. The TCM treatment plan was first included in the third edition and as much information has been gathered about the SARS-CoV-2 the TCM was recommended in every edition of the protocol. Different TCM strategies have been formulated to treat each stage of the disease[170]. TCM intervention in the early stages of the infection has shown increased cure rate, shortened disease course, fewer days of hospitalization and reduced mortality rate. COVID-19 can cause multi-organ failure and, ultimately, death by inducing hypersensitivity reactions and a cytokine storm. This is where TCM is efficient in battling the robust immune response by regulating the host inflammatory response via multicomponent, multitarget and multipathway mechanisms to alleviate the symptoms, prevent disease progression and complications, and also gain control of the virus suppression indirectly[171]. An academician of the Chinese Academy of Engineering stated that a TCM-oriented makeshift hospital led by Zhang Boli, had no patient developing severe conditions or progressing from mild to severe cases of the disease after receiving all-inclusive TCM therapies.

TCM methods comprise Chinese herbal medicines (CHMs), acupuncture, aromatherapy and some Chinese patented medicines. The CHMs exhibit unique therapeutic effects on various infectious diseases based on the holistic treatment concept and multitarget, multicomponent pharmacological characteristics[169]. If Chinese herbal medicines are used by Chinese herbal experts, it has been reported that this will result in no side effects which surpasses the benefits of modern medicines[165]. Using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform three CHM compounds were found to contain puerarin and uqercetin. Molecular docking analysis revealed that these compounds have good binding affinity for the ACE2 receptor, hindering the binding of the ACE2 receptor with the spike protein of the virus. Quercetin also has some potential to bind to the RBD domain of the S-protein indicating that it may neutralize SARS-CoV-2. These two compounds were found in one herb, *Radix bupleuri* (to satisfy the TCM theory, best results are expected when the two compounds reside in the same CHM, providing synergistic therapeutic effects to the patients) which also contains baicalin, which exhibits similar effects to

puerarin and uqercetin[172].

Decoctions are made using varieties of the Chinese herbal compounds including Huashi Baidu decoction, Qingfei Paidu decoction and Xuanfei Baidu formula. They provide immunity against the virus, enhance host immunity, reduce inflammation, lower lung pathogenesis, with occurrence of less liver and kidney damage, prevent worsening of the clinical manifestations and shorten the course of the disease and hospitalization. The efficacy of the Qingfei Paidu decoction was > 90%[173]. Other TCMs are Huoxiang Zhengqi with aniti-inflammatory effects, improvement in oxygenation indexes and systematic symptoms; Lianhua Qingwen inhibits pro-inflammatory cytokine production resulting in the protection of the lungs from pneumonia; Shufeng Jiedu inhibits virus proliferation and lastly Xue Bijing injection reduces multi-organ damage via anti-inflammatory and immunomodulation effects[171]. Chinese patented medicines are broadly being used due to their ready availability. COVID-19 diagnosis and treatment protocols have recommended the use of Chinese patented medicines at all stages of SARS-CoV-2 infection[173]. Lianhua Qingwen capsules are commonly used for common colds and influenza. They prevent the advancement of moderate cases to severe ones and prompt improvement in the clinical symptoms along with inhibition of SARS-CoV-2 replication. Also, use of Jinhua Qinggan granules along with routine treatment alleviates the symptoms and reduces the psychological anxiety levels in patients[174].

During the COVID-19 pandemic, TCM is the only treatment method that has been effective in China in contrast to modern medicines that have delivered only temporary relief to the suffering of COVID-19 patients. After close monitoring of SARS-CoV-2 patients receiving TCM treatment with and without modern medicine it has been concluded that the integrated use of the TCM with modern medicine under appropriate safety guidelines and measures can bring more rapid improved and permanent results[167]. According to the clinical experts who have been treating COVID-19 patients in Wuhan, including Professor Boli Zhang and Professor Xiaolin Tong, TCM should be used at the earliest possible stage of the disease to gain its therapeutic benefit[168]. All these significant and unique features of TCM make it the prime choice of treatment plan for combating an epidemic, while no dedicated drug is currently available except a few newly certified vaccines after phase 3 clinical trials.

10 CONCLUSIONS

SARS-CoV-2 has challenged humanity, creating a global pandemic with spontaneous mutations over time, and is actually an altered version of the previous SARS-CoV-1 with similarities to the MERS virus. It has been reported to infect the upper respiratory tract with manifestations of fever, dry cough, shortness of breath, fatigue and other symptoms. The fatality rate following severe infection is higher than in similar epidemics as there is no established vaccination or other treatment available. A number of recent studies have suggested that natural and modified antimicrobial peptides have adequate efficacy to suppress virus infections by blocking essential infection pathways by creating a cellular and molecular interaction in the human immune system against viruses. On the basis of this concept the induced immunization and antiviral infection prevention potentiality of bacteriocins have been summarized in this review and new pathways suggested for bacteriocin research to understand their use with other advanced technologies such as synthetic biology and nanotechnology in addressing the global threat of COVID-19. In addition, traditional Chinese medicine can also have a significant role if used appropriately with antimicrobial peptides against SARS-CoV-2 by blocking the virulent factors in the human respiratory system. To ensure maximum benefits, further research must be conducted on bacteriocins *in vitro*, *in situ* and *in vivo* in an integrative approach.

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Compliance with ethics guidelines

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