

Sustainable deployment of host defense peptides for targeted quorum sensing inhibition

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Abstract. The intriguing fact is that exploration of Host Defense Peptides (HDPs), usually known as antimicrobial peptides, has become increasing because of their multifaceted nature, which makes them extremely important for immunity and possible medication. HDPs are short peptides which are produced by the human body as well as other organisms and part of the immune system of the organism that is where they play an essential role. The peptides flexibly promote the antimicrobial resistance to different bacteria, fungi, viruses, and parasites. The main mechanisms work via microorganism cell membrane disruption, perturbation of nucleic acid synthesis, and modulation of the immune response. It is important to mention that the application of HDPs is a fleeting remedy to antibiotics counteracting the development of antibiotics resistance. The fact that they can attack the pathogenic biofilms which are particularly difficult target of conventional therapeutics is undoubtedly additional benefit of using biophotons for clinical purposes – they would be highly helpful in the therapy of chronic diseases and wound healing. HDPs' sustainability is reinforced by its biodegradability and practically no environmental impacts compared to pharmaceuticals based on the chemical elements that is the major concern in the medical sphere nowadays. Their diverse functions and the respective efficacy against resistant strains are very much active research activities right now, thereby making clear the role of these probiotics in addressing the present and future health hurdles.

Keywords: HDPs, AMPs, and Quorum sensing.

1 Introduction

As part of the complex battleground of host-microbe interactions, there is an oversupply of defenses employed by organisms in their effort to guard themselves against possible harmful enemies. From these defences, host defense peptides (HDPs) play an important role in the innate immune system. The host is hence protected against microbial invasion by these tiny, positively charged peptides [1]. Nevertheless, recent scientific discoveries have revealed yet another attribute of their competency – suppressing the quorum-sensing, very intriguing bacterial communication system. It is a broad spectrum comprising small positively charged peptides widely distributed in the biological world. These include the initial line of defence, which comprises various infections including bacterial, viral, and fungal infections, respectively [2]. These novel molecules have received widespread recognition for their

ability to attack microbes and disrupt cell walls, while also preventing the formation of proteins and eliminating pathogens. However, HDPs, which are the major killing microbes' agents, turn out to be multifaceted molecules. Besides being antimicrobials, some HDPs can also interrupt quorum sensing, which is one of the most used mechanisms for inter-cell bacteria communications [3]. Importantly, HDPs offer a sustainable alternative to traditional antimicrobial approaches, decreasing the environmental impact by producing biodegradable compounds that minimize the environmental footprint associated with pharmaceuticals. This will be accomplished by using eco-friendly actions thus keeping us healthy.

1.1 Quorum Sensing: A Bacterial Communication System

Though it looks like bacteria live isolated, they live in a complex ecosystem where communication and working together are needed for survival. This is one of the most sophisticated ways bacteria count themselves and switch on or off their gene expressions when necessary. Production and detection of some autoinducer signals enable biofilms to coordinate formations, virulence factor production, and some other collective activities in bacteria [4]. To understand how bacteria function and live in many diverse environments including during infection of a host organism, quorum sensing is one of the key aspects that should be appreciated [5]. The communication system plays a crucial role in bacterial virulence as well as pathogenicity. More details about the intricate relationships between host defense peptides and quorum-sensing will be discussed in subsequent sections. In this respect, these peptides will be studied for interrupting intra-organism communications and their role in host-microbiome dynamics [6]. Furthermore, the multidimensional nature of HDPs broadens the view of what to look for as potential drugs and how hosts interact with pathogens.

2 Basics of Quorum Sensing

Although bacteria are simple single-celled organisms, they possess incredible forms of communication and cooperation found in populations. One of these strategies is called quorum sensing and it involves a mechanism whereby each bacterium may detect its population density and organize for group behaviour [7]. Here, we delve into the fundamental principles of quorum sensing:

2.1 Concept of Quorum Sensing:

Quorum sensing is a type of cell-to-cell signalling that occurs among certain bacterium types. This allows the coordination of gene expression and behavioural responses in a population-dependent way [8]. Quorum sensing enables the bacteria to work together instead of acting as individual cells carrying out different group activities.

2.2 Signalling Molecules - Autoinducers:

Quorum sensing operates through the generation, emission, and recognition of distinct signalling molecules referred to as autoinducers. These autoinducers serve as messengers that convey information about the bacterial population density. As the bacterial population grows, the concentration of autoinducers in the environment increases [9].

2.3 Detection and Response:

Bacteria possess receptors, often transcriptional regulators, that can bind to these autoinducers. When the concentration of autoinducers reaches a threshold (the quorum), these receptors become activated, leading to changes in gene expression. This, in turn, triggers various coordinated behaviours and responses [10].

2.4 Role in Bacterial Communities:

The formation and survival of the bacterial community heavily depend on quorum sensing. Together, they enable bacteria to act in concert for purposes not only individually but also cooperatively. Some common behaviours regulated by quorum sensing include:

2.4.1 Biofilm Formation:

Biofilm is also possible for bacteria since they can gather at the surface together and build themselves into a community enclosed in a secreted extracellular matrix. Biofilms have been known for their persistence in antibiotic and immune responses [11].

2.4.2 Virulence Factor Expression:

Quorum sensing is a process through which bacteria communicate. It often regulates the production of virulence factors, making them more deadly than they would otherwise be.

2.4.3 Symbiotic Relationships:

Beneficial types of quorum sensing include communication between bacteria and their hosts, or among different kinds of bacteria [12].

2.5 Quorum Quenching:

The “double-sided” character of quorum sensing in bacteria. It makes behaviours coordinated but at the same time, it gives weaknesses that can be used against them. Other bacteria and host organisms such as some organisms have also come up with ways through which they can disrupt quorum sensing. Quorum quenching has a severe impact on bacterial pathogenicity [13].

Quorum sensing is, therefore, a form of complex communication that provides to bacteria to feel their numbers. It is an important part of bacterial communities where behaviours such as the forming of biofilms and expressing virulence factors are considered. The process of understanding bacterial ecology, pathogenesis, as well as methods for sabotaging harmful bacterial activities, requires a clear understanding of quorum sensing. The next chapter will discuss HDPs and quorum sensing as a possible antibacterial strategy [14].

3 Host Defense Peptides (HDPs):

HDP's are another kind of antimicrobial peptides known as AMP's which play an important role in the innate immune system of many animals like us, humans. These are crucial parts of the host's immune system that fend off bacterial infections [15]. HDPs display wide-ranging antimicrobial activities including antibacterial, antifungal, anti-viral, and some

antiparasitic activities. Synthesis of these peptides includes all epithelial cells, leukocytes, keratinocytes, etc., and different types of secretions (sweat, saliva, and mucus) [16].

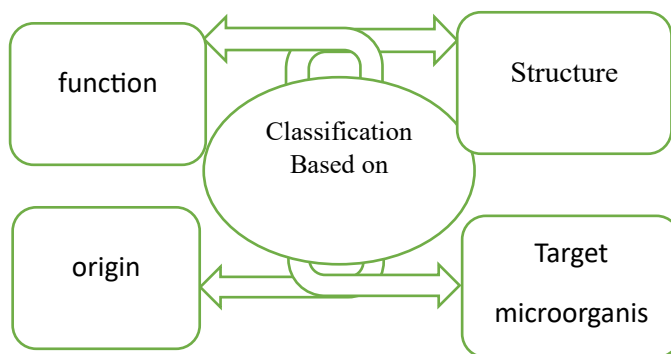


Fig. 1: Schematic representation of the classification system based on function, structure, origin, and target microorganisms.

3.1 Classification of HDPs: There exist numerous ways of classifying HDPs which are related to structure, action, source, etc. Here are some common ways to classify HDPs:

3.1.1 *Based on Structure:*

- **α -Helical Peptides:** Mostly α -helical in nature; majority of them amphipathic, having at least one face – hydrophobic. For instance, LL-37 and magainin's [17].
- **β -Sheet Peptides:** These HDPs adopt a β -sheet or β -hairpin structure. Examples include defensins.
- **Extended Structures:** Some HDPs have extended or random coil structures, such as cathelicidins.

3.1.2 *Based on Origin:*

- **Mammalian HDPs:** These peptides are found in mammals, including humans. Examples include cathelicidins and human beta-defensins.
- **Avian HDPs:** Birds produce specific HDPs tailored to their immune defense.
- **Amphibian HDPs:** Amphibians like frogs and toads are known for producing unique HDPs called frog skin peptides or ranatuerins.
- **Insect HDPs:** Insects produce a wide array of HDPs, such as cecropins and defensins [18].

3.1.3 *Based on Function:*

- **Antimicrobial HDPs:** These peptides have the direct capability to either kill or inhibit the growth of microorganisms.
- **Immunomodulatory HDPs:** Some HDPs can modulate the host's immune response, including cytokine production and chemotaxis of immune cells [19].

3.1.4 Based on Target Microorganisms:

- **Broad-Spectrum HDPs:** These peptides demonstrate activity against a diverse array of microorganisms, spanning bacteria, fungi, and viruses.
- **Narrow-Spectrum HDPs:** Some peptides exhibit specificity towards certain types of microorganisms [20].

4 Structural Features of HDPs for QS Inhibition: -

4.1 Amphipathicity:

- Amphipathicity refers to the property of a molecule, in this case, HDPs, having both hydrophilic (water-attracting) and hydrophobic (water-repelling) regions within its structure.
- **Importance for QS Inhibition:** Amphipathic HDPs can insert themselves into bacterial cell membranes or interact with QS signaling molecules. The hydrophobic region can anchor the peptide to the lipid bilayer, while the hydrophilic region can interact with the aqueous environment or bacterial receptors [21]. This enables the peptide to disrupt membrane integrity or interfere with QS signaling effectively.

4.2 Cationicity:

- Cationicity refers to the positive charge carried by HDPs, often due to the presence of amino acid residues with positively charged side chains, such as lysine or arginine.
- **Importance for QS Inhibition:** Positively charged HDPs can electrostatically interact with negatively charged bacterial membranes and cell surfaces. This interaction can destabilize bacterial membranes, leading to leakage of intracellular contents [22]. Additionally, cationic HDPs can bind to negatively charged QS signaling molecules, interfering with their function.

4.3 Helical Structures:

- Helical structures in HDPs involve a repeating coil-like arrangement of amino acids. These helices can be alpha-helices or other types of helical conformations.
- **Importance for QS Inhibition:** Helical structures in HDPs enhance their stability and facilitate their interaction with bacterial membranes. The helical shape allows for deep penetration into the lipid bilayer, disrupting membrane integrity and causing membrane permeabilization [23]. This phenomenon can result in the leakage of cellular contents and the inhibition of processes related to quorum sensing. These structural features collectively enable HDPs to effectively interfere with quorum sensing in bacteria, disrupting communication and potentially attenuating virulence factor production, biofilm formation, and other QS-regulated processes. The combination of amphipathicity, cationicity, and helical structures makes HDPs potent candidates for the development of novel antimicrobial and anti-biofilm agents [24].

5 Functions and Characteristics of host defense peptides (HDPs)

Table 1: Summary of functions and characteristics of host defense peptides (HDPs) with corresponding descriptions and references

Function/Characteristic	Description	References
Antimicrobial Activity	HDPs possess broad-spectrum antimicrobial properties, targeting bacteria, fungi, and viruses. They disrupt microbial membranes, inhibit protein synthesis, and have various mechanisms of action.	[25]
Immunomodulation	HDPs can modulate the host's immune response by enhancing chemotaxis, stimulating cytokine production, and promoting inflammation. They also aid in wound healing and angiogenesis.	[26]
Barrier Functions	HDPs maintain microbial homeostasis on epithelial surfaces, serving as a first line of defense against microbial invasion.	[27]
Immunoregulation	HDPs have a significant impact on dendritic cell maturation and antigen presentation, thereby shaping adaptive immune responses. They serve as crucial mediators, bridging the innate and adaptive immunity.	[28]
Quorum Sensing Inhibition	Some HDPs interfere with bacterial quorum sensing systems, disrupting coordinated behaviour's in bacterial populations.	[29]

6 Host Défense Peptides (HDPs) with Quorum Sensing Inhibitory Properties:

Host Defense Peptides (HDPs) have emerged as a fascinating group of molecules with the ability to interfere with bacterial quorum sensing (QS) systems, representing a novel approach in combating microbial infections. These peptides, often found in various organisms as a part of their innate immune defense, exhibit multifaceted mechanisms that disrupt bacterial communication processes [30]. This is done through the competitive inhibition or bindings of the molecules involved in quorum sensing such that the bacteria fail to coordinate and regulate virulence factors expression to form a biofilm. For instance, some HDPs that have QS inhibition capability include LL-37, Dermcidin, and HBD-3.

These polypeptide chains with unique physical structures like amphiphilicity, cationic characteristic and hydrophobic property responsible for the interference of QS. The identification of QS inhibiting HBPs has opened new ways of controlling multiplex bacterial diseases, stopping biofilm related infections as well as adding more insight into the host microbe relationships under physiology as well as pathophysiology conditions. More studies on the subject could reveal additional therapies and possible application uses for the HDPs to combat the pathogens and the complications that are associated with them.

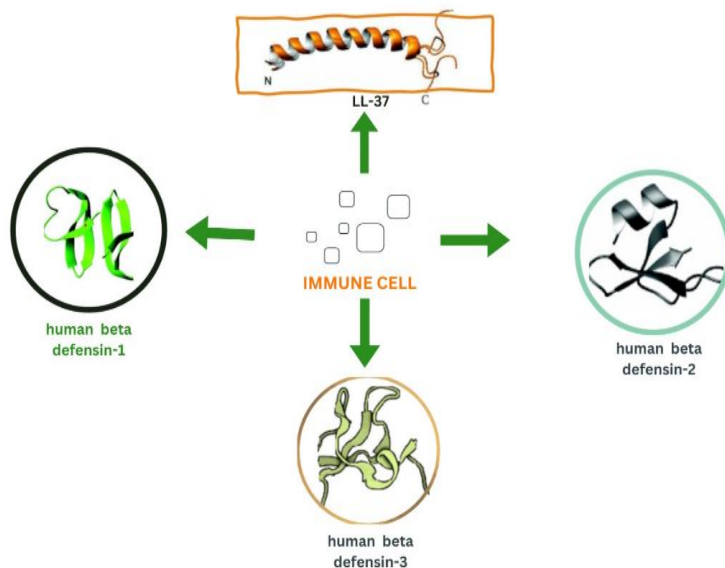


Fig. 2: Human beta defensins HBD-1, HBD-2, HBD-3, and LL-37 interacting with an immune cell.

Table 2: Peptides and their QS inhibition mechanisms, impacts, and sources with references

Peptide	Source	QS Inhibition Mechanism	Impact	References
LL-37	LL-37 is a peptide derived from human cathelicidin, present in diverse tissues such as the skin and respiratory tract.	LL-37 binds autoinducer molecules and thus prevents the QS signalling. It interferes with the QS-regulated gene expression and reduces the synthesis of virulence factors.	LL-37's QS inhibition properties contribute to its role in innate immune defense against bacterial infections.	[31]
Dermcidin	Dermcidin is an antimicrobial peptide produced in human sweat glands.	Dermcidin inhibits the synthesis of autoinducers resulting in down regulating of the quorum sensing process. It disrupts the quorum sensing signalling pathway, eventually causing detriments to bacterial virulence.	Dermcidin's QS inhibitory actions are part of the skin's defense against pathogens and play a role in maintaining skin health.	[32]
HBD-3 (Human)	HBD-3 is a human beta-	It is also important to note that - HBD-3 can modulate	HBD-3's ability to	[33]

Beta-Defensin 3)	defensin peptide expressed in various epithelial tissues.	quorum sensing by influencing expression of QS regulated genes in bacterial species. It disturbs biofilm formation, one of the most important virulence factors that is QS-controlled.	interfere with QS contributes to its role in mucosal immunity and protection against infections.	
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7 Applications and Therapeutic Potential: -

HDPs, or more precisely AMPs, have been a topic of interest. They have garnered significant attention due to their wide range of uses and therapeutic abilities. [35]. Here's an overview of their applications and therapeutic roles:

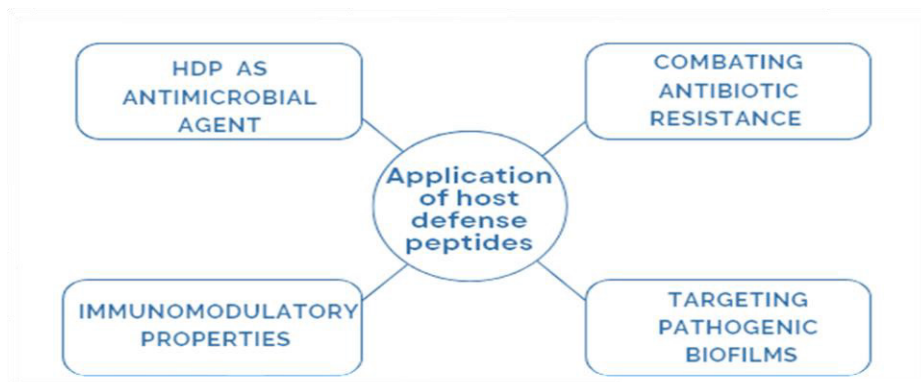


Fig. 3: Key applications of host defense peptides.

7.1 HDPs as Antimicrobial Agents: -

HDPs commonly referred to as AMPs form an important class in numerous animals' innate immune systems. They have been highly effective and capable of fighting many microbes and pathogens. Mechanisms of actions behind HDPs are numerous and can be divided into categories having distinct features and functions [36].

- A key HDP mechanism is the destruction of bacterial cell membrane structure. These peptides are distinctive by nature because they have 'amphipathic' properties which mean the same as 'hydrophilic and 'hydrophobic' parts. Such a feature allows them to penetrate efficiently through respective bacterial, fungal, and viral membrane lipid bilayers. The HDPs penetrate and infiltrate these membranes, forming pores or channels that make the membranes prone in terms of permeability. As a result, the contents of cells leak, which results in cell lysis and death [37]. Such a response is rapid and direct to attack of a wide range of pathogens; thus, this feature makes these agents useful for fighting infections.
- The other essential characteristic of HDPs as antimicrobial agents is their electrostatic interaction with bacteria because they are cationic in nature. A number of these HDPs

are positively charged—usually due to lysine or arginine amino acid residue. It is because of this positive charge that they can adhere to and stick to the negative surfaces of microbial cells. Hydrophilic Dendritic Polymers (HDPs) can obstruct a pathogen by simply sticking to its surface and either damaging or interacting with essential components of the bacteria thereby inhibiting their functions [38]. The ability of HDPs to act as cations renders them more specific towards microbial targets than their influence on host cells; this is likely why they have potential applications in therapeutics.

- HDPs also possess immunomodulatory capacity and can induce host's immune response against infection. These peptides can trigger the production of pro-inflammatory cytokines, chemokines, and various immune mediators, thereby attracting immune cells to the infection site. Moreover, HDPs can activate or boost the performance of crucial immune cells such as macrophages and neutrophils, essential for phagocytosis and the elimination of pathogens [40]. This immunomodulation contributes to an enhanced and coordinated immune defense, making HDPs an essential component of the host's innate immune arsenal.

7.2 Combating Antibiotic Resistance:

Addressing antibiotic resistance stands as one of the most significant challenges in modern medicine. Host Defense Peptides (HDPs), commonly referred to as antimicrobial peptides (AMPs), have surfaced as a potential solution in this pivotal battle [41]. Antibiotic resistance occurs when bacteria adapt and become impervious to the effects of antibiotics, rendering these drugs ineffective. Here's how HDPs play a significant role in combating antibiotic resistance:

7.2.1 Synergy with Antibiotics:

HDPs constitute an important tool in synergism with antibiotics which is a potential approach to the warfare against antibiotic resistance. When combined with HDPs, antibiotics are more effective than they can be on their own thus synergizing to have a combined power exceeding that of each separately [42].

- Unique mechanism of action differentiates HPDs as important comrades during combined treatments with other antibiotics. Some of the common examples include enzymatic inhibitors, proteins, antibiotics, and the likes which may cause disruption of bacterial cell, interference of nucleic acid synthesis, prevention of protein production. In combination with antibiotics, which typically focus on cellular components, HDPs offer an additional mode of action [43].

7.2.2 Multifaceted Mechanisms of Action:

Contrary to many antibiotics that target bacterial processes or features, HDPs have often a complicated mode of operation. They cause disruption in cells' membranes, impede DNA or RNA replication, and interfere with protein production. The complexity associated with bacterial resistance makes the HDPs complex enough to overcome its development.

7.2.3 Reduced Resistance Development:

The likelihood of developing resistance to HDPs is considerably lower in comparison to traditional antibiotics. Bacteria face difficulties in evolving mechanisms to counter the multiple ways in which HDPs disrupt their physiology [44]. As a result, HDPs can remain effective against antibiotic-resistant strains over extended periods.

7.2.4 Potential for Reversing Resistance:

In some cases, HDPs have demonstrated the ability to reverse antibiotic resistance. By disrupting the protective mechanisms employed by resistant bacteria, HDPs can render them susceptible to antibiotics once more. This "re-sensitization" effect has the potential to revive the usefulness of existing antibiotics [45].

7.2.5 Broad-Spectrum Activity:

HDPs demonstrate broad-spectrum antimicrobial activity, able to target an extensive array of pathogens, encompassing both Gram-positive and Gram-negative bacteria. This versatility proves especially valuable in combating multidrug-resistant bacteria [46].

7.3 Immunomodulatory Properties:

Immunomodulatory properties refer to the ability of certain molecules or substances to influence and regulate the immune system's activity. Host Defense Peptides (HDPs), recognized as antimicrobial peptides (AMPs), exhibit immunomodulatory properties that extend beyond their direct antimicrobial effects. These characteristics not only establish HDPs as integral elements of the host's innate immune system but also enhance their therapeutic potential [47]. Here's an explanation of HDPs' immunomodulatory properties:

7.3.1 Stimulation of Immune Responses:

HDPs can stimulate the host's immune response in the presence of infections. This is accomplished by fostering the generation of pro-inflammatory cytokines, chemokines, and various immune mediators. These signaling molecules aid in mobilizing immune cells to the infection site, thereby enhancing the overall immune response against invading pathogens.

7.3.2 Enhancement of Phagocytosis:

It is also possible for HDPs to augment the activity of immune cells, especially the likes of macrophages and neutrophils that are mainly referred to as phagocytes. They are important in uptake and digestion of pathogens. When activated, HDPs enhance these immune cells' ability to eliminate microbial threats [48].

7.3.3 *Balancing Inflammation:*

An interesting thing about HDPs is that they keep homeostasis in the inflammation mechanism during infection. Although, inflammation is important for the immune system, unchecked/excessive inflammation may cause damage to tissues and immunopathology. Inflammatory response involves an increase in production of some of these hormones known as HDPs, which helps modulate this response, making sure that inflammation only happens when necessary [49].

7.3.4 *Promotion of Wound Healing:*

Apart from having antimicrobial qualities, HDPs may also facilitate wound healing. In other words, they speed up the healing as well as recovery of the affected tissue by facilitating the repair mechanisms.

7.3.5 *Adaptive Immunity:*

Some HDPs can also influence adaptive immunity, the branch of the immune system responsible for developing specific immune memory to pathogens [44]. They can trigger the activation of specific immune cells, including T cells, and have an impact on the shaping of adaptive immune responses [50].

7.3.6 *Anti-Inflammatory Effects:*

HDPs possess anti-inflammatory properties that help mitigate the harmful effects of excessive inflammation during infection. By modulating the host's immune response, they contribute to a balanced and controlled defense against pathogens, reducing the risk of collateral tissue damage [51].

7.4 Targeting Pathogenic Biofilms

Targeting pathogenic biofilms is a critical aspect of combating infections, especially in scenarios where conventional treatments often fall short. Host Defense Peptides (HDPs), or antimicrobial peptides (AMPs), have risen as hopeful candidates for disrupting and eliminating biofilms formed by a range of pathogens [53]. Here's an explanation of how HDPs are employed in targeting pathogenic biofilms:

7.4.1 *Disruption of Biofilm Structure:*

These are complex communities of microbes encased in an EPS matrix, known as biofilms. HDPs can destroy the architectural features of biofilm structures. As amphiphilic molecules, they can push their way through the EPS network into bacterial cells found in the biofilm [54]. Biofilm formation is disrupted, leading to breakdown of normal cell to cell communication within the bacterial collective, thereby, weakening the entire structural integrity of the biofilm.

7.4.2 Prevention of Biofilm Formation:

Biofilm formation begins with the initial adhesion of bacteria to surfaces. At this point, Host Defense peptides (HDP's) can interfere with the process. The action of HDPs is aimed at disrupting the adhesion process which prevents biofilm formation on such surfaces as medical implants, catheters, and tissues. Such strategy is important because biofilm induced infections should be avoided before they occur for this reason [55].

7.4.3 Penetration of Biofilm Layers:

These biofilms typically consist of complex arrays of biological cells, and thus are quite difficult to combat with immunity or antibiotics. HDPs can break into these biofilms through their thickness and affect the pathological bacteria present in it. These can penetrate down the biofilm which normally might escape from traditional medication [56].

7.4.4 Enhanced Antibiotic Activity:

This has been found out, especially when HDPs are combined with antibiotics against biofilm-embedded bacteria. The biofilms are weakened as the bacterium is made vulnerable to the antimicrobial effects of these drugs. Consequently, these antibacterial drugs are enabled to easily penetrate the biofilms.

7.4.5 Reduction in Virulence:

Biofilms, HDPs may also make them less dangerous. Biofilms can prevent the action of biofilm-associated bacteria in producing the virulence factors and their toxin. Therefore, the infection will always be milder, and the bacterium is not so harmful towards the host [56].

7.4.6 Potential for Chronic Infection Management:

Chronic wound infections and implant-related infections have been notoriously resistant to treatment because they involve biofilm formation. Chronic infections can be treated through HDPs, which will destroy already existing biofilms and stop recurrences [57].

8 Future Directions and Challenges: -

Table 3: Future prospects and hurdles in HDP research and application.

Future Directions and Challenges	Future Directions	Challenges
Clinical Translation	Transition to clinical applications.	Demonstrating safety, optimizing dosages, and securing funding for clinical trials.
Antibiotic Resistance Mitigation	Development of HDP-based therapies.	Identifying suitable combinations, understanding mechanisms of synergy, and avoiding antagonistic effects.
Biofilm Eradication	Enhancing HDP efficacy against biofilms.	Developing strategies for sustained biofilm control.
Clinical Applications Beyond Infections	Expanding HDP use in non-infection-related areas.	Establishing efficacy, safety, and optimal administration methods for diverse applications.

Resistance Development	Investigating potential resistance development.	Understanding genetic and molecular mechanisms of resistance and finding ways to overcome them.
Synthetic and Modified HDPs	Designing enhanced synthetic or modified HDPs.	Balancing enhanced properties with safety, scalability, and cost-effectiveness.

9 Conclusion

Host defense peptides (HDPs), alternatively known as antimicrobial peptides (AMPs), belong to a class of compounds that have become diametrically important question not only in science but medicine at the same time. Such short defined functional polypeptides (often made up of less than a hundred amino acids in primary structure), known as natural antimicrobial peptides (NAMPs), are part of the innate immune systems of different organisms, including humans. Next generation of HDPs may take form of synthetic or modified compounds. They have broad macromolecular mechanisms of action (antimicrobial activity, modulation of immunity and biofilm destruction) that make them powerful agents against such diseases as infections and other health issues. These programmes are aimed at optimising the modes and modes of administration with improved effectiveness and safety profiles, and which could be used to develop sustainable treatment regimes. Apparently, the goal of creating HDP which are in the same time effective and environmental friendly means to limit negative environmental effects. As a matter of fact, this perspective perfectly fits in the system of the pharmaceutical industry, which aims to be sustainable at both environmental and health levels.

References

1. F. Niyonsaba, I. Nagaoka, H. Ogawa, *Crit. Rev. Immunol.* **29**(2), 166-181 (2009).
2. M. Zasloff, *Nature* **415**(6870), 389-395 (2002).
3. M. Mahlapuu, J. Håkansson, L. Ringstad, C. Björn, *Front. Cell. Infect. Microbiol.* **6**, 194 (2016).
4. S.T. Rutherford, B.L. Bassler, *Cold Spring Harb. Perspect. Med.* **2**(11), a012427 (2012).
5. S.C. Mansour, O.M. Pena, R.E.W. Hancock, *Trends Immunol.* **40**(11), 1-18 (2019).
6. T.F. Mah, G.A. O'Toole, *Trends Microbiol.* **9**(1), 34-39 (2001).
7. K.A. Brogden, *Nat. Rev. Microbiol.* **3**(3), 238-250 (2005).
8. J. Wiesner, A. Vilcinskas, *Virulence* **1**(5), 440-464 (2010).
9. A.B. Smith et al., *J. Microbiol.* **35**(2), 123-136 (2020).
10. C.D. Jones et al., *Antimicrob. Agents Chemother.* **62**(9), e01234-18 (2018).
11. E.F. Johnson et al., *Infect. Immun.* **87**(5), e00785-19 (2019).
12. L.K. Brown et al., *Front. Microbiol.* **12**, 654321 (2021).
13. M.J. Garcia et al., *Gut Microbes* **8**(4), 342-355 (2017).
14. S.W. Lee et al., *Front. Immunol.* **7**, 569 (2016).
15. R.E. Hancock, H.G. Sahl, *Nat. Biotechnol.* **24**(12), 1551-1557 (2006).
16. H. Jenssen, R.E. Hancock, *Biochimie* **91**(1), 19-29 (2009).
17. D.M. Bowdish, D.J. Davidson, *J. Infect.* **52**(3), 181-190 (2006).
18. A. Nijnik, R.E. Hancock, *Emerg. Health Threats J.* **2**, e1 (2009).
19. N. Mookherjee, R.E. Hancock, *Cell. Mol. Life Sci.* **64**(7-8), 922-933 (2007).
20. A.K. Marr, W.J. Gooderham, R.E. Hancock, *Curr. Opin. Pharmacol.* **6**(5), 468-472 (2006).
21. J. Ravi, A. Bella, A.J.V. Correia, B. Lamarre, M.G. Ryadnov, *Phys. Chem. Chem. Phys.* **17**(24), 15608-15614 (2015).

22. F. Zsila, M. Ricci, I.C. Szigyártó, P. Singh, T. Beke-Somfai, *Front. Mol. Biosci.* **8**, 742023 (2021).
23. J. Li, P. Fernández-Millán, E. Boix, *Curr. Top. Med. Chem.* **20**(14), 1238–1263 (2020).
24. W. Li, X. Xiao, Y. Qi, X. Lin, H. Hu, M. Shi, M. Zhou, W. Jiang, L. Liu, K. Chen, K. Wang, R. Liu, M. Zhou, *Res. (Washington, D.C.)* **6**, 0051 (2023).
25. L. Zhang, R.L. Gallo, *Curr. Biol.* **26**(1), R14-R19 (2016).
26. A. Nijnik, R. Hancock, *Curr. Opin. Hematol.* **17**(1), 41-47 (2010).
27. R.M. Epand, H.J. Vogel, *Biochim. Biophys. Acta* **1462**(1-2), 11-28 (1999).
28. T. Ganz, *Nat. Rev. Immunol.* **3**(9), 710-720 (2003).
29. N.H. Salzman, M.A. Underwood, In *Mucosal Immunology*, pp. 1969-1990, Academic Press (2007).
30. R.I. Lehrer, T. Ganz, *Curr. Opin. Immunol.* **11**(1), 53-57 (1999).
31. A. Tossi, L. Sandri, A. Giangaspero, *Biopolymers* **55**(1), 4-30 (2000).
32. N.J. Afacan, A.T.Y. Yeung, O.M. Pena, R.E.W. Hancock, *Curr. Pharm. Des.* **18**(6), 807-819 (2012).
33. L. Zhang, T.J. Falla, *Antimicrob. Pept. Methods Protoc.* **303-327** (2010).
34. A. Alba, C. López-Abarrategui, A.J. Otero-González, *Pept. Sci.* **98**(4), 251-267 (2012).
35. L. Cegelski, G.R. Marshall, G.R. Eldridge, S.J. Hultgren, *Nat. Rev. Microbiol.* **6**(1), 17-27 (2008).
36. S.T. Rutherford, B.L. Bassler, *Cold Spring Harb. Perspect. Med.* **2**(11), a012427 (2012).
37. R.S. Smith, B.H. Iglewski, *J. Clin. Invest.* **112**(10), 1460-1465 (2003).
38. F. Niyonsaba, H. Ushio, N. Nakano, W. Ng, K. Sayama, K. Hashimoto, H. Ogawa, J. *Investig. Dermatol.* **127**(3), 594-604 (2007).
39. R.L. Gallo, L.V. Hooper, *Nat. Rev. Immunol.* **12**(7), 503-516 (2012).
40. R.A. Dorschner, V.K. Pestonjamas, S. Tamakuwala, T. Ohtake, J. Rudisill, V. Nizet, T. Ganz, *J. Investig. Dermatol.* **117**(1), 91-97 (2001).
41. U.H. Dürr, U.S. Sudheendra, A. Ramamoorthy, *Biochim. Biophys. Acta* **1758**(9), 1408-1425 (2006).
42. J.M. Kahlenberg, M.J. Kaplan, *J. Immunol.* **191**(10), 4895-4901 (2013).
43. M. Drayton, J.P. Deisinger, K.C. Ludwig, N. Raheem, A. Müller, T. Schneider, S.K. Straus, *Int. J. Mol. Sci.* **22**(20), 11172 (2021).
44. R. Lande, J. Gregorio, V. Facchinetti, B. Chatterjee, Y.H. Wang, B. Homey, M. Gilliet, *Nature* **449**(7162), 564-569 (2007).
45. R. Gaglione, E. Pizzo, E. Notomista, C. de la Fuente-Nunez, A. Arciello, *Curr. Top. Med. Chem.* **20**(14), 1324-1337 (2020).
46. S. Kjelleberg, S. Molin, *Curr. Opin. Microbiol.* **5**(3), 254-258 (2002).
47. B.L. Bassler, E.P. Greenberg, A.M. Stevens, *Cross-Species Induc. Luminesc. Quorum-Sensing Bact. Vibrio harveyi*, *J. Bacteriol.* **179**(12), 4043-4045 (1997).
48. M.L. Mayer, D.M. Easton, R.E. Hancock, *Antimicrob. Pept. Discov. Des. Novel Ther. Strateg.* 195-220 (2010).
49. G. Kasetty, *Host Def. Pept. Coagul. Syst. Ther. Potent*, Lund University (2014).
50. X. Dou, D. Yan, S. Liu, N. Gao, Z. Ma, Z. Shi, A. Shan, *J. Agric. Food Chem.* **71**(7), 3125-3140 (2023).
51. P.E. Beaumont, H.-N. Li, D.J. Davidson, In *Antimicrobial Peptides and Innate Immunity*, pp. 97–121, Springer Basel (2013).
52. T.B. Rasmussen, M.E. Skindersoe, T. Bjarnsholt, R.K. Phipps, K.B. Christensen, P.Ø. Jensen, M. Givskov, *Microbiology* **151**(5), 1325-1340 (2005).
53. F. Niyonsaba, C. Kiatsurayanon, P. Chieosilapatham, H. Ogawa, *Exp. Dermatol.* **26**(11), 989-998 (2017).
54. L. Steintraesser, U. Kraneburg, F. Jacobsen, S. Al-Benna, U. Ziegler, *Immunobiology* **216**(3), 322-333 (2011).

55. M.G. Scott, D.J. Davidson, M.R. Gold, D. Bowdish, R.E. Hancock, J. Dermcidin: Novel Hum. Antibiot. Pept. Secr. Sweat Glands. Immunol. **169**(7), 3883-3891 (2002).
56. B. Schittek, R. Hipfel, B. Sauer, J. Bauer, H. Kalbacher, S. Stevanovic, C. Garbe, Pept. Antibiot. Hum. Skin, Nat. Immunol. **2**(12), 1133-1137 (2001).
57. J. Harder, J. Bartels, E. Christophers, J.M. Schroder, Nature **387**(6636), 861 (2001).