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Review

Phage-tail-like bacteriocins as a biomedical platform to counter anti-microbial resistant pathogens

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ABSTRACT

Phage Tail Like bacteriocins (PTLBs) has been an area of interest in the last couple of years owing to their varied application against multi-drug resistant (MDR), anti-microbial resistant (AMR) pathogens and their evolutionary link with the dsDNA virus and bacteriophages. PTLBs are defective phages derived from *Myoviridae* and *Siphoviridae* phages, PTLBs are distinguished into R-type (Rigid type) characterized by a non-flexible contractile nanotube resembling *Myoviridae* phage contractile tails, and F-type (Flexible type) with a flexible non-contractile rod-like structure similar to *Siphoviridae* phages. In this review, we have discussed the structural association, mechanism, and characterization of PTLBs. Moreover, we have elucidated the symbiotic biological function and application of PTLBs against MDR and XDR pathogens and highlighted the evolutionary role of PTLBs. The difficulties that must be overcome to implement PTLBs clinically are also discussed. It is imperative that these issues be addressed by academics in future studies before being implemented in clinical settings. This article is novel in its way as it will not only provide us with a gateway that acts as a novel strategy for scholars to mitigate and control the uprising issue of AMR pathogens but also promote the development of clinical studies for PTLBs.

1. Introduction

Bacteriophages have tail-like structures which can serve as machinery to transport DNA to the target organism. Phages like *Myoviridae* and *Siphoviridae* possess the functional ability to penetrate the bacterial cell envelope to overcome anti-microbial resistant AMR [1]. Phage tail-like bacteriocins (PTLBs) are referred to as defective prophages, phage remnants or tailocins that are structural homologs to bacteriophage tails. They are extensively found in eubacteria, which has evolved independently over time and have the ability to produce bacteriocins. PTLBs act like a class of novel anti-bacterial agents constituting approximately 8–14 polypeptide subunits with a molecular weight of more than 106 Da. PTLBs encoded in the bacterial genomes are the same as of phage tail structures and the genes present in these regions encodes

Abbreviations: AHL, N-acyl-homoserine lactone; PTLBs, Phage tail-like bacteriocins; RBPs, receptor binding proteins; MDR, Multi-Drug Resistant; AMR, Anti-microbial Resistance; XDR, Extensively Drug Resistant; LPS, Lipopolysaccharides; Cryo-EM, Cryogenic Electron Microscopy; ssDNA, Single stranded DNA; RBP, Receptor binding protein; CD, *Clostridium difficile*; CDI, *Clostridium difficile* infection; PAK, *Pseudomonas aeruginosa* strain K; PA14, *Pseudomonas aeruginosa* strain 14; PAO1, *Pseudomonas aeruginosa* strain 1; DNA, Deoxyribonucleic acid; CDC, Centre for Disease Control and Prevention; STEC, Shiga toxin-producing E. coli; USA, United States of America; WHO, World Health Organization; EHEC, *Enterohemorrhagic Escherichia coli*; lmaA, *Listeria monocytogenes* gene B; lmaD, *Listeria monocytogenes* gene D.

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proteins and chaperones aiding to catalyze structure formation [2]. PTLBs are induced by mitomycin C through the DNA damage or SOS response in bacteria, where it kills the competing bacteria via the release of diffocin and disruption of the membrane potential (Fig. 1) [3]. During the process of bacteriophage progeny formation in the bacteria body, matured bacteriocins get discharged into the surrounding medium by the lysis of the producer cell after the assembly of intracellular particles, to kill nutrient-competing bacteria in the same niche. The genetically identical sister cells of the producer are repellent to the anti-bacterial activity of the produced PTLB, which gives them a competitive advantage to colonize the niche [4]. This kind of death mediated by PTLBs is often referred to as altruism since the cells are subjected to death by the anti-bacterial particle to provide a competitive and biological advantage to the identical sister cells [4].

Although there have been studies informing about the antibacterial mechanism of different types of PTLBs like R-type and F-Type, the majority of explanations refer to R-Type. It has been studied that the antibacterial action of R-Type PTLBs mediates through the binding of PTLBs to a target cell occurs via Receptor binding proteins (RBPs). It induces rapid death of the target via recognition of receptors present on the surface of the target bacterial cell [5]. This occurs through the sheath and tube contraction in R-type PTLBs to drive the inner core material of the enveloped cell disrupting the membrane potential of bacterial cells. The membrane potential of the bacterial cells gets dissipated as ions flow across the cytoplasmic membrane through the channel created by the PTLBs leading to the death of the enveloped cell [3,6]. Therefore, the complex association between the sheath and the tube plays a critical role in the killing efficiency of R-type PTLBs. Owing to their excellent killing capacity, these PTLBs have the potency to treat bacterial infections. F-type bacteriocins are similar to R-types which kill their target cell upon contact but their mode of mechanism is not yet clear, but it is assumed that it also occurs through the dissipation of the cell membrane potential as an effect of the creation of ion channels in the cell envelop [2]. Till now pieces of information to understand the synergistic biological functions, molecular mechanism, and application of PTLBs are limited [5]. They possess a potent bactericidal activity, as even one particle is enough to kill an entire cell as an antibacterial therapy against multi-drug resistant (MDR) and Extensively Drug-Resistant (XDR) pathogens [7]. Several advantages of PTLBs have been reported compared to existing antimicrobial compounds. These include its ability to be utilised as a biocontrol agent while being extensively diverse in nature. Moreover, it could be not only be tailored to enhance interbacterial competition but also to increase usage against a wide range of bacteria using multiple cell lysis mechanism[8].

In the review, we have highlighted the application, structural biology, evolutionary relationship, and the characterization of PTLBs. PTLBs can be utilized as an antimicrobial against AMR and XDR pathogens upon the interaction between the eukaryotic host and the bacterium. The clinical significance and the challenges of the application of PTLBs has been vividly elucidated in this article.

2. Evolutionary link with bacteriophage

In the microbial world, PTLBs exist in multiple types of forms where each type of PTLBs shares a common ancestor with other different types of bacteriophage tail. The different phage tail structures like PS17, TP901–1-, and lambda-like phage tails are analogous to R-type pyocins, F-type monocins, and F-type pyocins, respectively (Fig. 2). In the case of pyocins produced by P. aeruginosa, a third S-type corresponding to colicin-like proteins is described which is not like phage-tail like structures. The evolution of many structural and functional motifs of phage tails and phage tail-like bacteriocins have occurred parallelly [1]. A certain phage tail-like bacteriocin (Mu-like) was observed in *Pseudomonas syringae* at a genomic position similar to that of the two types of PTLB (R- and F-type) [9]. Similarly, Monocins produced by the foodborne human disease *L. monocytogenes*, resemble the tail structures of TP901–1 phages [10].

The structure of PTLBs shows resemblance to those of phage tails observed in electron microscopy exhibiting an evolutionarily link to these phage organelles (Fig. 3) [11]. Electron microscopic studies revealed the structural identities of R-type pyocin and *Pseudomonas syringae* PS17 phage, wherein six fibers are attached to the tail structure homologs to R1 pyocin [12]. The length of the phage PS17 tail was larger than that of pyocin R1 and both (the phage tail and the pyocin) exhibited cross-reactivity with each other causing receptor specificity [13]. The identified receptor for R-pyocin is lipopolysaccharide which interacts with PS17. The morphology and receptor specificity of these two suggests that they share common features [14]. Cross-reactivity and genetic relativeness were observed between the *Pseudomonas aeruginosa* phage and the R-type pyocin [15]. The interaction between pyocin and *Pseudomonas* phage and the interchangeability with tail fibers provided genetic evidence suggesting that R-type pyocin of *P. aeruginosa* PAO, R2, and PS17 tail components are interchangeable via complementation studies [16]. The non-ideal intrinsic charge of *Pseudomonas* phage tail structures reduced bactericidal action by hundred times [17].

A certain phage having serological cross-reaction was observed in F-type pyocin and thus these pyocins were assumed to have an evolutionary relationship with the tail structures of phage *Pseudomonas aeruginosa*[18]. Further, cross-reactivity was also observed between a certain temperate phage of *Pseudomonas aeruginosa* and an R-type

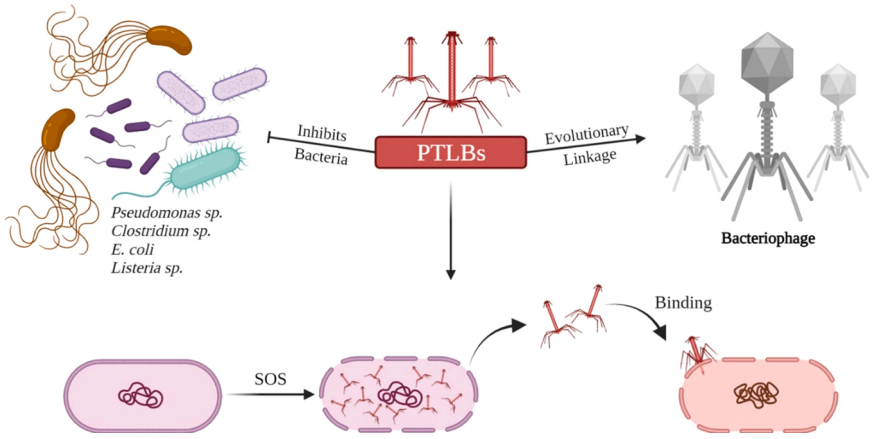

Fig. 1. Phage tail structures are analogous to R-type pyocins, monocins and F-type monocins. The evolution of many structural and functional motifs of phage tails and phage tail-like bacteriocins have occurred parallelly. PTLBs inhibit bacteria like *Pseudomonas sp., Clostridium sp., E. coli, Listeria sp.,* etc. via SOS induction in bacteria-containing genes to release PTLBs which consequently binds to the unprotected cells without the genes.

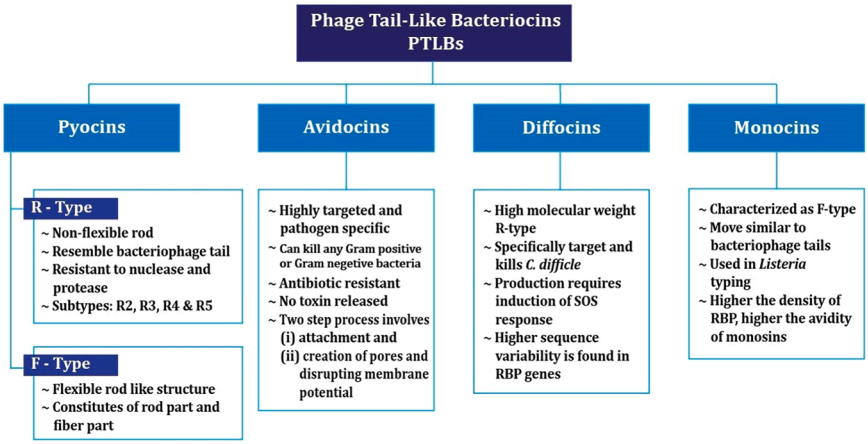

Fig. 2. Types of PTLBs: Pyocins produced from *Pseudomonas aeruginosa* are further classified into R-type, F-type, and S-type PTLBs. Avidocins as an R-type PTLBs engineered from diffocins is a promising candidate against *Clostridium difficile* infection. Diffocins are R-type bacteriocins analogous to R-type pyocin that originated from *Clostridium difficile*. Monocins obtained from *Listeria monocytogenes* represent a new class of PTLBs that are recently discovered and possess homology to a temperate phage called TP-901–1 phages.

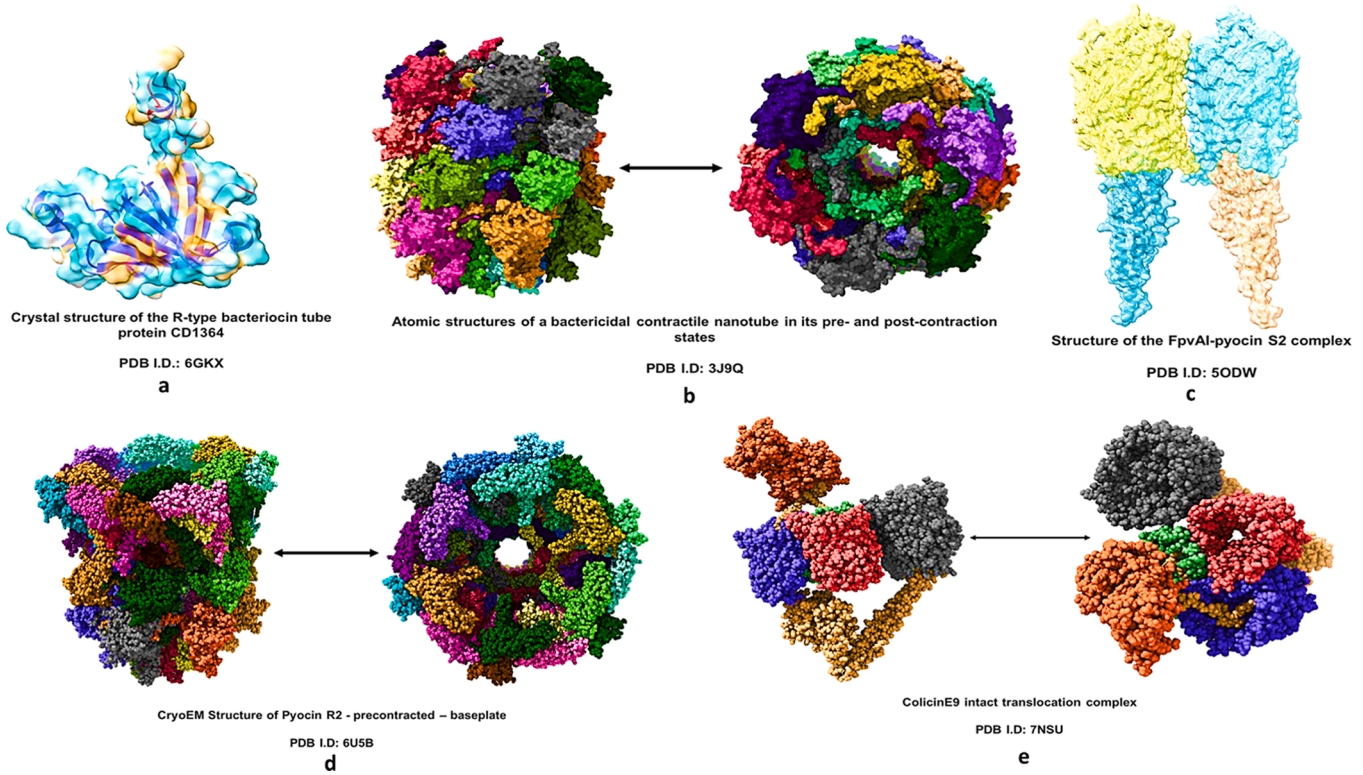

Fig. 3. : Structural organization of bacteriocins. (a) Crystal structure of R-type bacteriocin tube protein CD1364. (b) Atomic structure of a bactericidal contractile nanotube in its pre- and post-contraction states. (c) Structure of the Fpv AI-pyocin S2 complex. (d) Cryo-EM structure of Pyocin R2-precontracted baseplate. (e) Colicin E9 intact translocation complex.
(a) Adapted from PDB:6GKX. (b) Adapted from PDB:3J9Q. (c) Adapted from PDB:5ODW. (d) Adapted from PDB: 6U5B. (e) Adapted from PDB:7NSU.

pyocin-related phage [19]. Nakayama et al. investigated the relation between bacteriophages and pyocin through the nucleotide sequences of R- and F-type pyocin located on the chromosome of PAO1. The results demonstrated the relation of R-type with P2 phage and F-type with lambda phage. The induction of temperate or lysogenic phages by SOS response leads to the production and release of PTLBs by lysis supporting the fact that they descended from defective prophages lacking capsid genes and replication abilities [18]. Various adaptions are assumed to have occurred after their genesis, which rendered them more effective at destroying membrane potential and cells. Nevertheless, structure comparison studies among R-type pyocin, secretion systems, and phage tails suggested that they share a common lineage that presumably precedes phage with tail structures [20]. Hence, a different hypothesis suggests that these structures might have come from a common ancestor. (Table 1).

3. Structural organization

Among PTLBs, only R- and F-type pyocins have been studied thoroughly. The PTLBs discovered were probably the R-type pyocins, also referred as pyocines from *P. aeruginosa* in the year 1952 [26]. With biochemical-based studies, the very first work started with the involvement of purification of PTLBs and characterization of their physical properties [27]. Electron microscopic studies made it clear that PTLBs is similar to the tail structures of phages. Moreover, purification techniques exhibited that one pyocin particle is effective enough to kill

Table 1
Origin of Phage tail like bacteriocin.

Types	Evolutionary relation	Origin	Bacterial Target	Specificity (Bactericidal activity)	References
F-Types	*Siphoviridae*	*Pseudomonas aeruginosa.* Other bacterial species: *Pseudomonas flourescens, Staphylococcus aureus, Listeria monocytogenes.*	Gram-negative bacteria, such as *Neisseria, Haemophilus, Camphylobacter.*	Kill cells by dissipation of the membrane potential, leading to cell death.	[21,22]
R-Types	*Myoviridae*	*Pseudomonas aeruginosa.* Other bacterial species: *Pseudomonas flourescens, Yersinia enterocolitica, Clostridium difficile.*	Gram-negative bacteria, such as *Neisseria, Haemophilus, Camphylobacter.*	Kill cells by dissipation of the membrane potential, leads to cell death.	[23–25]

an entire bacterial cell. Among the two major types of pyocin, the R-types are the only ones whose structural studies have been done beyond basic electron microscopy [27]. R-type pyocins have been classified as R1, R2, R3, R4 and R5 into 5 different types according to the structural variations. The difference primarily lies in the C terminus of the tail fiber which confers target-strain specificity [28]. The three-dimensional (3D) model of R2 pyocin constitutes three major parts namely collar, trunk, and baseplate [28]. The R-type pyocin comprises a core or the collar domain present at one end of the structure, whereas the trunk diameter is about 65 Å present at the periphery (Fig. 3). The collar domain bridges a hollow tube with a contractile sheath [29]. The collar possesses a hexameric structure and each of its monomers possess two domains; one is globular and the other is the beta-hairpin domain, joined by an extended loop. The inner tube is extended by the collar and tethered to the sheath and thus, the tube would be prevented from its dissociation from the sheath post-contraction (Fig. 4). The trunk is present intermediate to the baseplate and the collar portion which gets contracted in a post-contracted state causing the central tube to get exposed. The baseplate part of a pyocin is present at the bottom and comprises eight different protein subunits, namely, ripcord, Tri1a, Tri1b, Tri2, sheath initiator, hub, glue, and spike.

The central part of the base plate is formed by the ripcord protein with the central spike complex lying at the bottom, the tube-sheath, and the trunk formed at the top whereas the rest of the baseplate including glue, triplex, and sheath initiator surrounds it [29]. The structure of R-type pyocin possesses a core with a tube-like structure wherein the tube does not contain possess surface characteristics and is featureless (Fig. 4). The assembly element of the pyocin tube constitutes a ring-like structure constituting six subunits of tube protein. The ring structures depict complementary either as negatively or positively surface charge on their contacting interfaces causing an electrostatic dipole required for directional self-assembly [28].

A trimeric pointed tail-spike protein with an iron moiety at its tip remains attached to this core near the baseplate [32]. A layer of sheath surrounds the core region wherein enormous globular bulges constitute the sheath protein subunits causing ridges intermediate of the grooves. The sheath protein constitutes of N- and C-terminal domain ranging from residue 21–280 and 281–361, respectively, and an extensive arm ranging from residues 2–20 and 362–386 at both the terminal of the polypeptide chain [28]. The length of the sheath or the assembled core in an uncontracted form is almost about 120 nm and the baseplate structure present at the periphery comprises 11 polypeptides with a diameter of 240 Å [2]. The central spike protein is connected to the inner surface of the baseplate ring via spokes and six tail fibers protrude out from the external surface of the base plate wherein the tail fibers serve as receptor binding proteins [2].

When the sequences of the tail fibers of all the five R-types pyocins were compared to C-terminal divergence, varied specificities of the target receptor were observed [33]. Different chaperone proteins are encoded by different types of pyocin where protein is not a structural part required for the tail fiber assembly. Chaperones possess specificity for the tail fiber C-terminal receptor-binding region required for the assembly of the pyocins and the formation of active particles during the creation of novel pyocins [33]. Chaperones are crucial for R-type pyocins assembly, specifically in tail fiber assembly. The chaperones of the tail fiber of R1 and R2 pyocin exhibit divergence at their C-termini that facilitates the assembly or folding of their tail fibers. Similarly, a divergence was exhibited in the R5 tail fiber at the C-termini and in its chaperone from that of the R2 tail fiber [33].

R-type pyocin constitutes a ssDNA, which is with the genome sequences of some filamentous bacteriophages rather than any pyocin genes. These DNA is assumed to have descended from a contaminating bacteriophage [34]. Structures of the core or sheath assembly as revealed by Cryogenic Electron Microscopy (Cryo-EM) depict the contraction mechanisms and interactions between the sheath and the core [28]. The arranged subunits of the sheath proteins show a change in

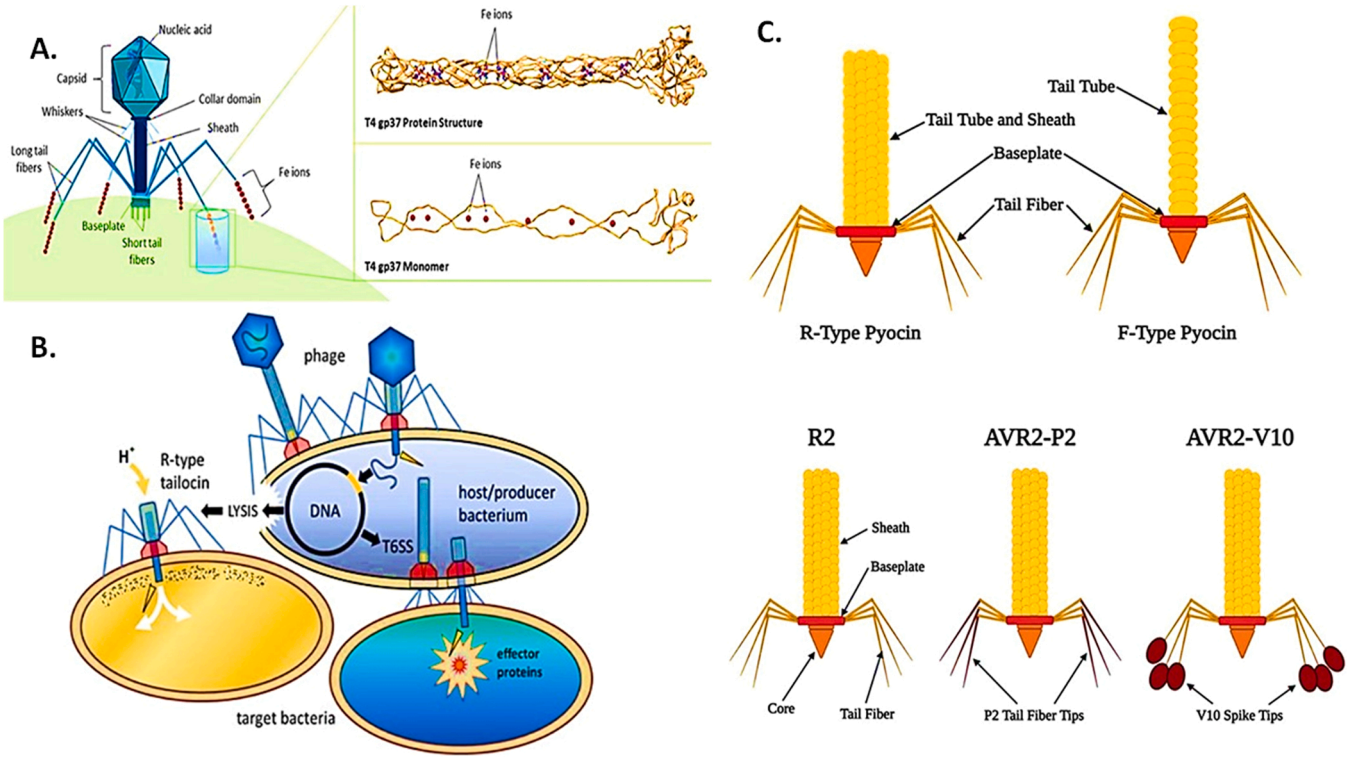

Fig. 4. (A) Structure of bacteriophage and engineered Phage with tailocin. (a) Structure of a typical bacteriophage belonging to the *Myoviridae* family. (B) A schematic representation of bacteriophages with two tail-like contractile phage particles is illustrated. (C) Structural association of Phage tail like bacteriocin; Structure of R-types is similar to *Myoviridae* phage tails, consisting of a long tube structure surrounded by a contractile sheath, connected to the baseplate structure at one end; Structure of F-types homologous to *Siphoviridae* phage tails. It is composed of a rod part and a fiber part having a tube without a sheath and are non-contractile structures attached to the baseplate at the distal end; Schematic representation of R-type pyocin structures. R2 is the wild type and is capable of killing some *P. aeruginosa* strains. Using the tail fiber of phage P2, AVR2-P2 are engineered pyocins that has been retargeted to kill some rough strains of *E. coli*. The modified pyocin was identified in[31] is AVR2-V10, which has the phage V10 tail spike fused to the pyocin tail fiber and is selective for *E. coli* strains that express the O157 antigen.
(a) Adapted with open access permission from [30]. (b) Adapted with open access permission from [31].

their conformation upon contraction followed by an 85-degree turn, reduction in sheath length, and expansion in diameter of the sheath which causes it to disengage from the tube and forces the tube or core downward after a particle binds to the cell. The inside of the core of the tube is negatively charged that making DNA translocation tedious [2]. Contractile R-type pyocins cause disruption of membrane potential and respiration for cell death [31]. Thus, the potent mechanism of killing is proved by the fact that just a single pyocin particle is effective enough to kill an entire bacterial cell.

4. Mechanism of action of PTLBs

PTLBs, also called tailocins, are narrow-spectrum antibacterial agents that lead to depolarization of the host membrane and kill bacterial cells [35]. One of the critical determinants shared by both PTLBs and phages is receptor-binding domains (RBPs) that identify particular receptors on cell surfaces such as proteins, polysaccharides (lipopolysaccharide, capsule), pili or flagella [2,5,36]. PTLBs are tailed phages without the head, and the tail varies from simple tail tip to complex base plate. Phage tails are quite tricky and serve as the mechanism to build the connection to bacterial hosts to initiate infection [37]. Tail proteins are diverse and may include different structures, including tail fibers and tail spikes capable of recognizing most host surface components [38].

Ackermann et al. examined 6200 phages using electron microscopy and found that over ninety percent comprised tailed phages in the *Caudovirales* order (myophages, podophages, sisophages) [39]. The interactions between these phage tail proteins and bacterial receptors determine the host specificity and range. Specific known receptors in *P. aeruginosa* are O-antigen of LPS and type IV pili. M22 and MPK7 are the *P. aeruginosa* phages that utilize the type IV pili as their receptors. The absence of the pilA gene in *P. aeruginosa* hosts makes it resistant to infection by these phages [40,41]. Further investigation accompanied with targeted research needs to be done for determining a coherent relationship between host immunity and PTLBs.

The mechanism of action for PTLBs includes the binding of particles to lipopolysaccharide (LPS) present on the cell surface through RBPs in tail fibers causing sheath contraction (Fig. 5). Furthermore, it forces the internal core into the cell envelope via iron-tipped tail spike proteins through the inner membrane [33]. The flow of ions across a channel disrupts the concentration gradients in the membrane causing cell death. The bactericidal activity of R-type bacteriocins is identical to *Myoviridae* phages that transport DNA into cells. The same mechanism applies to the bactericidal activity of T4 ghost phages wherein the phages do not have DNA [42]. R-type pyocin; when acts against *N. gonorrhea* causes the cell to lyse and exhibits bactericidal activity via a single-hit process [43]. The endogenous gonococcal autolysin action releases nucleic acid causing the cell to lyse post-pyocin-based inhibition. A muramidase-like enzyme in R-type pyocin is accounted for the rapid lysis of gonococcal cultures at high concentrations [43]. The R-type pyocin against *N. gonorrhea* causes the cell to lyse through an overabundance of cellular lytic enzymes produced by the species. F-type PTLBs unlike the R-types lack a contractile system of mechanism and are unable to penetrate through the membrane. F-types PTLBs secrete a single particle that is efficient to kill an entire bacterial cell by forming a channel in the inner membrane and disrupting respiration and membrane potential [44].

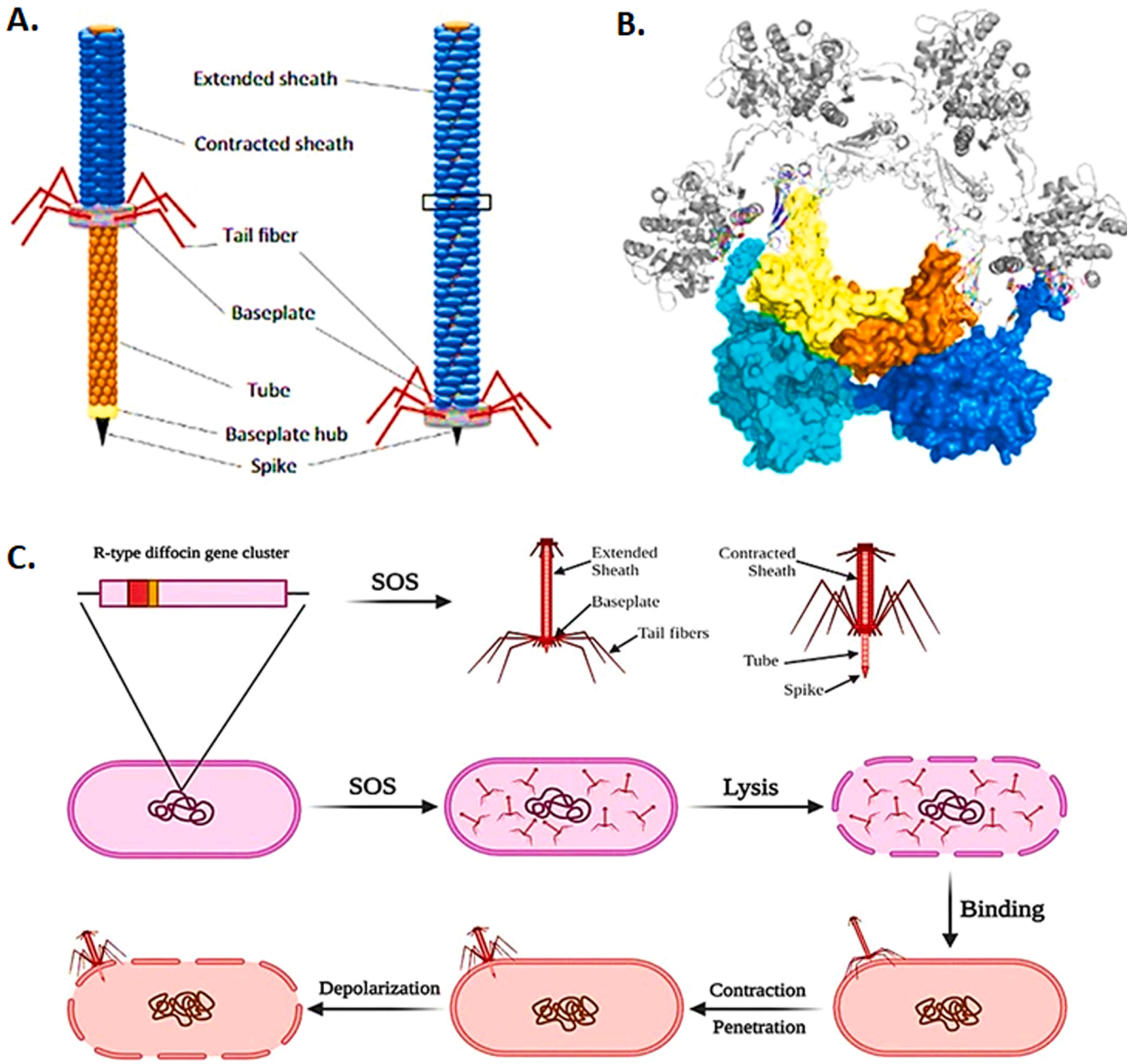

Fig. 5. : Structure and mechanism of a Bactericidal Tailocin. (A) The structure consists of a rigid tube (orange subunits), contractible sheath (blue subunits), lipopolysaccharide (LPS)-targeting tail fibers (red) attached to the baseplate (gray), and spike (black) connected via the baseplate hub (pale yellow) to the central tube; (B) Tail-tube architecture of pyocin R2 in extended conformation (EMDB-6270, PDB 3J9Q) with top view of a transverse section showing a hexameric disc. Two sheath protomers (cyan and blue) and two tube protomers (yellow and orange) are shown in surface representation; the other subunits (cartoon) are shown in gray (sheath) and white (tube); (C) Mechanism of action of PTLB for pathogen clearance as reported in. The genome of the *Clostridium difficile* strain constitutes CD630 and a 25-gene cluster encoding the R-type diffocin causing cell lysis post-SOS induction. It binds closely related but unprotected *C. difficile* strains to cause contraction of the diffocin sheath (red) to drive the tube (light orange) through the wall of the attacked cell for cell death by dissipation of the membrane potential.

This type of major protein possesses a part of the tube and membrane-spanning areas encoded by both the R-type pyocins and F-type pyocins. Moreover, these proteins could be inserted into the inner membrane for DNA translocation and are responsible for the tube or sheath length determination and causing pore formation in the inner membrane of both R- and F- types [2,45].

5. Characterization of PTLBS used for anti-microbial activity

5.1. Pyocins

A bacteriocin originating from strains of *Pseudomonas aeruginosa* was named pyocin owing to its capability to produce pyocins from *P. aeruginosa* species via pyocinogeny[46]. Pyocins are species-specific antibiotics produced by the bacterium itself. The synthesis of pyocin cells is inducible [47]. The DNA damaging agents trigger the regulator genes present near structural genes. They are unique polypeptide toxin that kills other strains from the same species (Fig. 6). The location of various structural genes are on the chromosome of R-type, S-type, and F-type pyocins [47,48]. The fixation on a specific receptor requires prior penetration of pyocins into the cells. The R-types are found to be similar to *Myoviridae* phage tails and the F-types to *Siphoviridae* prophage tail structures. Only the C terminal region differs in both of them and is responsible for target-strain specificity [18]. Due to their high killing

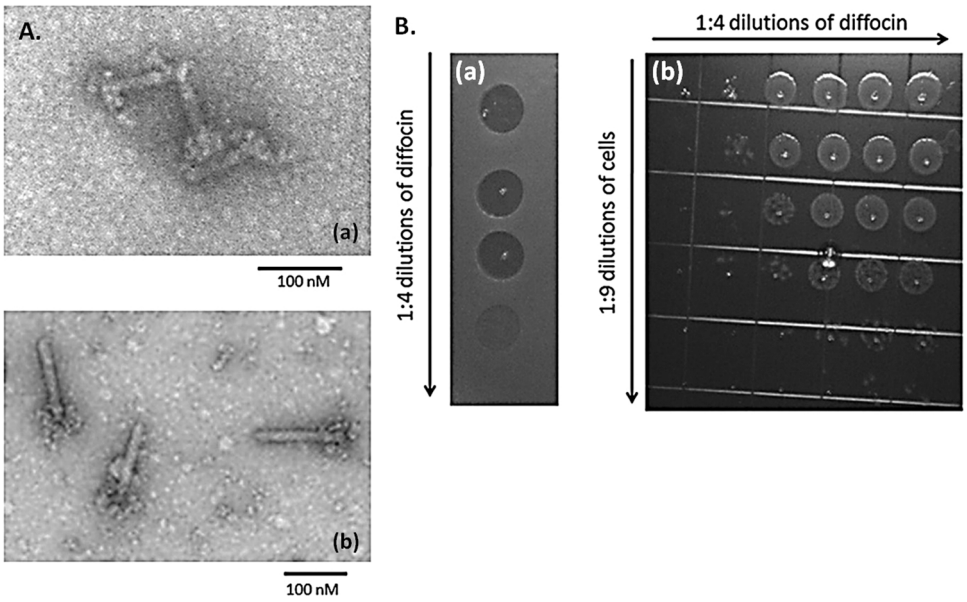

Fig. 6. : Role of Diffocins in inhibition of *C.difficile.* (A)Electron Microscope images of Diffocins when isolated from (a) CD44 and (b) strain. (B) Bactericidal activity of Diffocins causing *C.difficile* inhibition in (a) lawn assay and (b) liquid survival titration assay.
Adapted with open access permission from [59].

capacity, these pyocins are nowadays in great demand for antimicrobial and bioengineering applications [49]. Moreover, considering the advancement in the microbiological researches in different types of bacterial strains, these pyocins can be proved as advantageous [50].

Around 200 R-pyocin particles are produced by a single bacterium of *Pseudomonas aeruginosa* with sub-types of R2, R3, R4, and R5 pyocin [51, 52]. They constitute a non-flexible rod-like structure while sharing a close morphological resemblance to the tail of a bacteriophage. The R-types constitute a long tube structure surrounded by a contractile sheath possessing RBPs (tail fibers) connected to the baseplate structure at one end. All R-type pyocins are resistant to nuclease and protease to promote cell death within 20 min due to depolarization of cytoplasmic membrane for pore formation. Vibriocin is an example of R-type contractile bacteriocin from the bacteria *Vibrio cholerae,* which is one of the oldest PTLBs characterized after pyocins [53]. This bacteriocin constitutes a double hollow cylinder with a contractile inner and outer sheath accompanied by an inner core containing nucleic acid. Vibriocins are sensitive to proteolytic enzymes that require an active oxidative phosphorylating and protein-synthesizing cell to exert their activity [3]. Vibriocin was isolated and studied under an electron microscope with negative staining to determine its role in pathogenicity and the mechanism by which it induces cell death [54].

F-type pyocin has a flexible non-contractile rod-like structure bearing a resemblance to phage tails with RBPs attached to the baseplate at the distal end and a fiber section having a tube without a sheath [55]. The chemical composition of the filaments of the fiber part determines the difference between F-type pyocins and their specificity of attachment.

5.2. Avidocins

Avidocin is an engineered protein designed to be highly targeted and pathogen-specific bacteria, thereby avoiding damage to off-target bacterial species [56]. Avidocins are promising therapeutic agents that show a close resemblance to natural viruses that infect *C. difficile* (bacteriophage). These Avidocins constitute naturally occurring bacteriocin fused to RBPs of *Myoviridae* constituting with a needle inside a spring-loaded sheath (Fig. 6). When they bind to the bacterium of the cell surface the sheath contracts and injects the needle through the cell membrane, thereby killing the bacterium [56]. They are unaffected by antibiotic-resistance mechanisms and can be tailored to kill any gram-positive or gram-negative pathogens [57]. Moreover, avidocin proteins do not trigger the release of any toxins upon killing the bacteria and are biodegradable [58]. Thus, there is no disruption to the health-promoting bacteria within each person. This led to the construction of Av-CD291.2 a CD prototype against *Clostridium difficile* that causes nosocomial infections worldwide. Avidocin-CD involves a two-step process that includes an attachment to the target bacterium and then disruption of the membrane potential by creating pores on the target bacterium for its lysis. The precise killing activity and antibacterial properties aforementioned suggest Avidocin-CDs be effective and thereby encourage their further development as oral human therapeutics [56].

5.3. Diffocins

Diffocins are high-molecular-weight bacteriocins, analogous to R-type pyocin and are produced by *P. aeruginosa* (Fig. 6). Diffocins are derived from *C. difficile* and are developed to destroy *C. difficile*[59]. The genetic locus of these Diffocins is known to be common among the species. The active Diffocins are produced from the identification of the genetic locus encoding it and subsequent cloning from *C. difficile* for expressing it in *Bacillus*. The potent killing mechanism of bacteria by a single R-type bacteriocin makes them potential prophylactic agents for preventing CDI (Fig. 2). Upon induction of SOS response, some strains of *C. difficile* produce phage tail-like particles for *C. difficile* isolates clearance [60]. Initially, RBPs bind to the cognate cell-surface receptors on a target bacterium to determine the killing specificity of the bacterium. This mechanism is potent due to high sequence variability between RBP genes which makes Diffocins a potential prophylactic agent against CDI [60].

5.4. Monocins

Monocins or listeriocins are characterized as F-type bacteriocins first reported in 1961 and are found to be analogous to colicin-like *B. subtilis* (Fig. 2). These are bactericidal compounds produced from *Listeria monocytogenes* upon induction of SOS response [61,62]. Furthermore,

they exhibited flexible, non-contractile tails and were investigated to be more similar to bacteriophage tails. The receptor-binding domain (RBP) of monocin can be engineered to re-target its killing spectrum. The higher the density of RBPs, the higher the avidity of the monocin to the receptor [44]. This led to the irreversible binding of monocin and the target receptor, for bactericidal properties. Monocins possess the potent bactericidal activity and are extensively used in *Listeria* typing but none have been examined in detail [63].

6. Applications of Phage tail-like bacteriocin (PTLBs)

Given the importance and efficacy of PTLBs, they are considered for applications like antibacterial agents and can play an important weapon against Antimicrobial resistance (AMR). AMR is the ability of a microorganism to escape or protect itself from the drugs tailored to mitigate them [64,65]. It is considered a global public health concern and thus continues to threaten our ability to treat common infections. AMR is a natural phenomenon that can affect people at any stage and occurs naturally through genetic changes over time. Antimicrobial misuse and overuse, sanitation, lack of access to clean water, and hygiene are the leading causes of antimicrobial resistance [66]. In 2001, the World Health Organization (WHO) acknowledged the need for a global effort and provided a framework of interventions to limit the emergence and stop the spread of antimicrobial-resistant bacteria [67]. According to the US Centre for Disease Control and Prevention (CDC) 2019 Antibiotic Resistance (AR) threats reports, more than 2.8 million antimicrobial-resistant infections occur yearly in the U.S.A and worldwide, resulting in approximately 35,000 deaths [68]. Therefore, innovative approaches such as introducing new vaccines and developing rapid diagnostic tools are required to save unnecessary use of antibiotics, thereby curbing the spread of AMR.

6.1. PTLBs as an antimicrobial

Bacteriocin and bacteriophage when used as monotherapy have posed certain limitations and advantages. The engineering of the tail of the phage to integrate bacteriocins may serve as an ideal candidate to mitigate the long-lasting problem of AMR pathogens (Fig. 7). The clinical significance of the application of PTLBs to combat MDR and XDR pathogens has been summarized in Table 2. MDR and XDR has become an uprising issue that needs to be addressed. Bacteriocin and bacteriophage when used as monotherapy have posed certain limitation and advantages. The engineering of tail of phage to integrate bacteriocins may serve as an ideal candidate to mitigate the long-lasting problem of AMR pathogens (Fig. 7). The clinical significance of the application of PTLBs to combat MDR and XDR pathogens has been summarized in Table 2.

6.1.1. Pseudomonas aeruginosa

Pseudomonas aeruginosa is an aerobic, opportunistic, rod-shaped bacterium found in the soil and water causing inflammation and sepsis [72]. According to the Centre for Disease Control and Prevention (CDC), approximately 2700 people died in the United States, and 32,600 infections were estimated among hospitalized patients due to *P. aeruginosa* in the year 2017 [73]. The infection is often treated with antibiotics but high resistance to those has rendered it ineffective [74]. The mechanism of AMR for *P. aeruginosa* includes the production of antibiotic degrading enzymes or mutating antibiotic targets. This led to further research in designing novel bactericidal agents effective against such pathogens. Bird et al. for the first time in 1969 utilized PTLBs to be an anti-infective agent and exhibited that they could rescue chick embryos infected with *P. aeruginosa* [75]. After a few years, Merrikin et al. detected the effect of pyocin prepared from mitomycin C-induced culture of *P. aeruginosa* against three strains of *P. aeruginosa* but effective against two of the strains (Fig. 7) [69].

In another investigation, Haas et al. investigated the prophylactic effect of pyocin against *P. aeruginosa* in a murine model. A single injection of pyocin was exhibited to be therapeutically effective against all strains of *P. aeruginosa* in in vitro study and lasted for at least four days [76]. Moreover, pyocin used was concentrated but not purified indicating the effect was mainly related to the activity of pyocin and not to some other components. PTLBs have also been used for bacterial typing in *P. aeruginosa and L. monocytogenes* due to their high strain specificity (Fig. 8) [10]. A modified pyocin typing method was exhibited to be effective against O-serotyping. The value of O-serotyping is limited to strains belonging to the same serotypes but provides a rapid indication of antigenic differences. Pyocin typing is less tedious and time-consuming, thus a better suitable typing system for epidemiological studies of *P. aeruginosa* [77]. However, neither of the two methods provides all the basic requirements of the ideal typing system for *P. aeruginosa.* The pyocin sensitivity of the gonococcal typing scheme and its potential usefulness as an epidemiological tool was examined which revealed that the sensitivity of pyocin extracts could be used to differentiate and cause pathogen clearance of *Gonococcal* strains.

6.1.2. E. coli

Escherichia coli is gram-negative commensal bacteria found extensively in the vicinity of animal intestines [79]. Even though most of the strains of *E. coli* is non-toxic, some have been associated with severe food poisoning caused by strains such as Shiga toxin-producing *E. coli* (STEC) [80]. The CDC estimates that the *E. coli* O157:H7 serotype is responsible for 36% of 26,5000 cases of STEC infections in the USA annually.

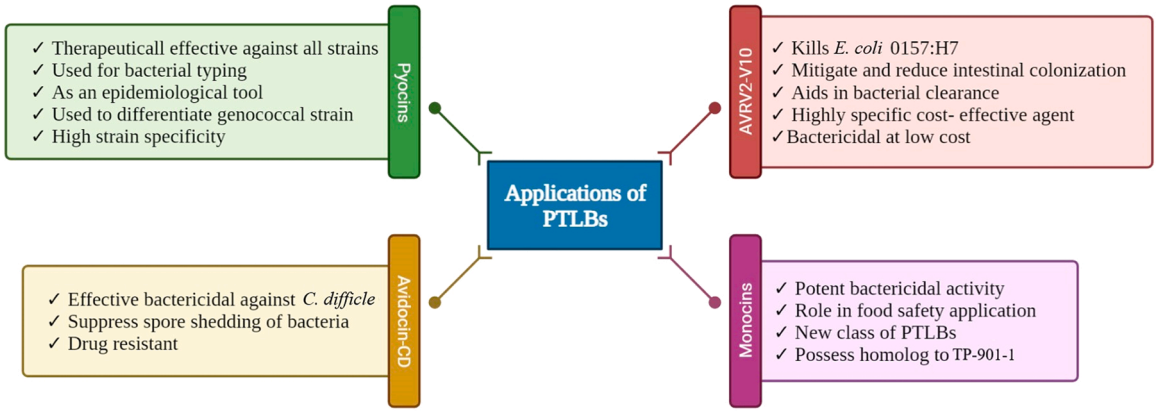

Fig. 7. : Application of PTLBs: Pyocins – species-specific antibiotics produced by the bacterium *Pseudomonas aeruginosa.* Avidocin-CD - an engineered protein designed to be pathogen-specific against *Clostridium difficile.* AVRV2-V10 - genetically engineered R-type pyocins are considered to be effective against *E. coli* O157:H7. Monocins – a bactericidal compound produced from *Listeria monocytogenes* upon induction of SOS response.

Table 2
Anti-microbial application of Phage tail-like bacteriocins.

The bacterial producer of the original wild-type PTLB	The target pathogen of the engineered PTLB	The type of modification introduced by engineering	Application	References
Pyocins	*Pseudomonas aeruginosa*	*In-vitro*	• Therapeutically effective against all strains of *P. aeruginosa*. • Used for bacterial typing. • Usefulness as an epidemiological tool.	[10,69]
R-type tailocin	*Pseudomonas aeruginosa*	*In-vivo*	• R-type tailocin cause lysis of the targeted pathogen by puncturing their cell membrane	[70]
AVR2-V10	*Escherichia. coli*	*In-vivo*	• Good candidates to kill E. coli O157:H7. • Mitigate and reduce intestinal colonization. • Aids in causing bacterial clearance from infected patients.	[31]
Avidocin-CDs	*Clostridium difficile*	*In-vivo*	• Effective bactericidal particle to treat *C. difficile* infection. • Suppresses the proliferation and pore shedding of the bacteria.	[56,60]
Monocins	*Listeria monocytogenes*	NA	• Potent bactericidal activity. • Role in the food-safety application.	[44]
Maltocin	*E.coli and* S. *maltophilia*	in-vitro	• Potent bactericidal activity. • Aids in preventions of MDR infections.	[71]

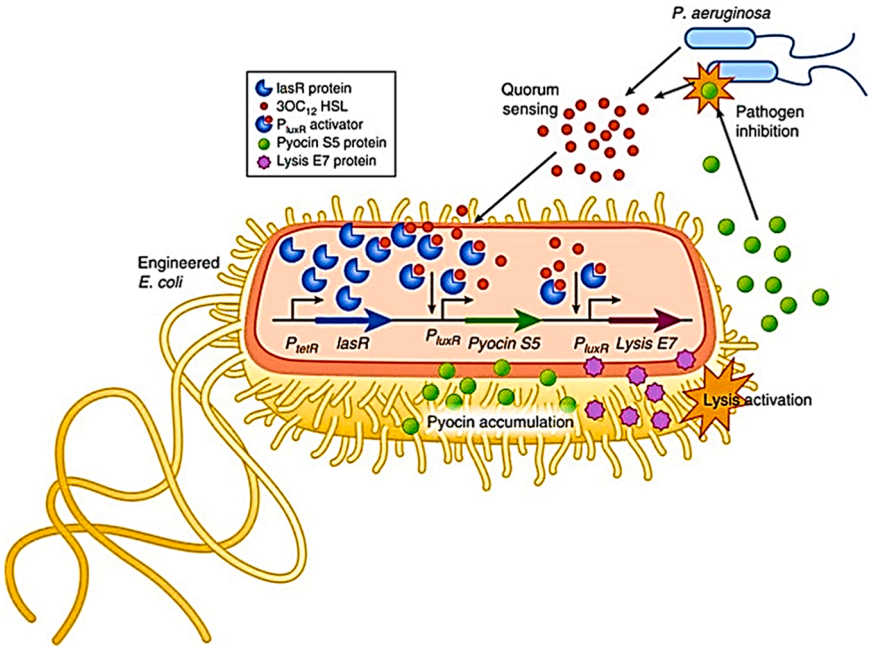

Fig. 8. : Anti-Pathogen Detection and Response System of *E. coli* that carries genes to allow it to detect and kill target *Pseudomonas* sp. The tetR promoter controls the lasR gene which upon contact with 3-oxo-C12 HSL activates the luxR promoter to produce Pyocin S5 and lysis protein E7 to kill *P. aeruginosa.* Adapted with open access permission from [78].

Abdominal cramps and bloody diarrhoea are considered to be common symptoms of STEC [31]. *E. coli* serotype O157:H7 is primarily transmitted to humans through the ingestion of contaminated foods. Antibiotics are ineffective against STEC infection and possess an enhanced risk of toxins.

AVR2-V10 is a genetically engineered R-type pyocins are considered to be effective against *E. coli* O157:H7 [31]. However, AVR-V10 is engineered by targeting R-type pyocin to the tail spike of O157-specific V10 of *E. coli O157:H7* and it has proven to be a promising prophylactic against *E. coli* O157:H7 intestinal colonization. This engineered pyocin is a highly specific cost-effective agent, bactericidal at low concentrations, and without any toxicities (Fig. 7) [31]. It is predicted that the whole Shiga toxin-generating *E. coli* O104:H4 strain can be covered by a panel of 4–6 engineered pyocin. AVR2-V10 aids in causing bacterial clearance from infected patients, thus minimizing human-to-human transmission. In a similar study conducted in an infant rabbit model, AVR2-V10.3 an alternative form of AVR2-V10 was effective in preventing diarrhoea induced by *E. coli O157:H7* by reducing the severity of disease symptoms (Fig. 9). Moreover, AVR2-V10.3 is active in the intestine and curtails the severity of intestinal inflammation caused by *E. coli* O157:H7 [81].

6.1.3. *Clostridium difficile*

Clostridium difficile is a bacterial pathogen causing life-threatening diarrhoea and is known to be the most common cause of infection in hospitals around the world [82]. Due to a large number of pore shedding, it has become difficult to eradicate them and limit human transmission. According to CDC, the United States reported 12,800 deaths and 223,900 infections among hospitalized patients due to *C. difficile* in 2017 [82]. Treatment with antibiotics is rendered ineffective as it leads to off-target effects putting the patients at risk of contracting a new infection or re-infection by disrupting protective microbiota and thus,

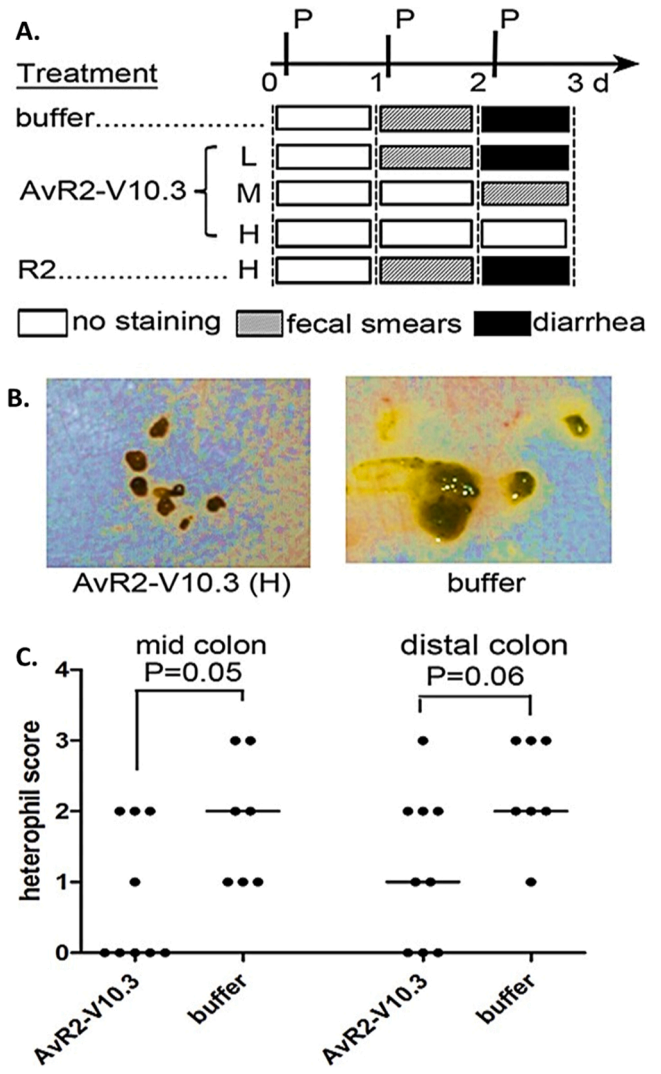

Fig. 9. : Influence of Phage tail-like bacteriocins to combat *E.coli* infections. E. coli O157:H7 infection is prevented or mitigated by prophylactic injection of AvR2-V10.3. (A) A diagram depicting the onset of diarrhoea and the timing of an E. coli O157:H7 infection, as well as preventative treatment procedures. After inoculating infant rabbits with E. coli O157:H7 at time zero, low (L; 1011 KU), medium (M; 2 1011 KU), and high (H; 1012 KU) doses of AvR2-V10.3 or R2 pyocin were given at the respective times (P). The appearance of faecal stains and diarrhoea in treated rabbits was compared to sick rabbits who were only given buffer. Diarrhoea symptoms were monitored daily. (B) Representative faeces from E. coli O157:H7-infected rabbits treated with 3 doses of 1012 AvR2-V10.3 KU (left) or buffer alone at 3 days post-infection (right). (C) Heterophil scores for mid- and distal colonic tissue isolated from *E. coli* O157:H7-infected rabbits treated with 1012 KU of AvR2-V10.3 or with buffer. Each symbol represents the score for an individual rabbit, and each bar shows the median. Heterophil scores were analyzed using the Mann-Whitney U test in Prism software; the sums of ranks differed significantly ($P \leq 0.05$) for the mid-colons of animals treated with AvR2-V10.3 versus those that received buffer. (a) Reproduced with open access permission from [81].

causing simple diarrhoea to severe life-threatening manifestations such as colitis and toxic megacolon[82,83].

Gebhart et al. utilized Avidocin-CDs as an R-type PTLBs to be a promising candidate against *Clostridium difficile* infection (CDI) (Fig. 10). Avidocin-CDs is a genetically engineered Diffocins from the CD4 strain of *C. difficile* that causes pathogen clearance of BI/NAPI/027 type strains through receptor binding protein (RBP) by replacing the previous one through modified Diffocins (Fig. 7) [56]. Avidocin-based prophylaxis suppresses the proliferation and pore shedding of the bacteria and when administered in drinking water prevents the colonization of *C. difficile* by hindering the transmission of disease, and preserving the diversity of gut microbiota. However, Avidocin-CDs are no exception to the emergence of resistance for any antibacterial agent, but the uniqueness of the bacterial surface receptor limits the spread of drug resistance making it an effective prophylactic agent [83]. In another study, open reading frames 1359–1376 of Diffocins were identified and found to be common among species, also the large structural protein product of this gene which is likely to be the receptor-binding domain demonstrated to be an effective bactericidal particle to treat infections and decolonize asymptomatic carrier individuals [59].

6.1.4. *Listeria monocytogenes*

L. monocytogenes is an intracellular, facultative, gram-positive pathogen responsible for causing severe infection listeriosis, with a high mortality rate (20–30%) [84]. According to World Health Organization (WHO), around 0.1–10 cases per year are reported worldwide. The pathogen survives and replicates in phagocytic and non-phagocytic cells and is ubiquitously a food-borne pathogen proliferating at refrigeration temperature [85]. The pathogenicity is multifactorial and is affected by haemolysin, surface components, capacity for intracellular growth, iron compounds causing infections through direct transmission from infected animals to farmworkers and veterinarians. It has become challenging to remove them from the food chain due to its adaptability to environmental challenges [85].

Monocins represent a new class of PTLBs that possess homology to T901–1 phages (Fig. 11). They are obtained from *L. monocytogenes* upon induction of the SOS system. Lee et al. cloned monocins from *L. monocytogenes* and expressed them in a heterologous host *Bacillus subtilis* producing targeted bactericidal particles via engineered receptor-binding protein to change the bactericidal spectrum (Fig. 7) [44]. When combined with the wild-type monocin M35152, the resulting engineered monocin M35152-A118 is considered to possess potent bactericidal activity against foodborne *L. monocytogenes* strains (4b and 1/2a) and thus, signifying its role in the food-safety application [44].

Based on the above findings, it could be concluded that the application of PTLBs has posed serious impact of AMR pathogens. Even though the findings infer clinical significance of PTLBs, more research in experimental models and clinical settings needs to be done. Overall, the volume of research on this subject is currently insufficient to justify this multi-hoop approach. Due to the enormous structural and functional variety within both bacteriocins and bacteriophages, discovering common patterns is a major bottleneck. Nonetheless, when fresh experimental data and a better acquaintance of the mechanisms underlying synergy, a detailed idea about the application of PTLBs will emerge.

7. Altruistic activity of PTLBs

Even though PTLBs produced by sister cells are generally resistant to cells, they are released into the medium through the lysis of individual cells causing cell death to provide sister cells a competitive advantage [44]. This altruism is exhibited by PTLBs in numerous studies for sister cells in *P. aeruginosa*, *Xenorhabdicin nematophila*, and *Rhizobium lupine.*

The R-type pyocin production provided a competitive growth advantage to investigate the competitive growth advantages or disadvantages among the strains of *P. aeruginosa* (PAK, PA14, PAO1) in mixed culture. The role of pyocin in such competitive growth advantages in *P. aeruginosa* was explored [40]. It was well known that strain PAO1 and strain PA14 outcompete the strain PAK causing complete loss of the strain in mixed cultures[28]. The competitive growth advantage shown by PAO1 and PA14 is attributed to a secreted bactericidal pyocin, whose production is observed early during the growth phase in the planktonic culture for killing [86]. Despite the R-type pyocin mutant losing its competitive advantage over the susceptible strain, the F-pyocin mutant was still able to outcompete the vulnerable strain. PA14's competitive advantage over the strain appears to be dependent on its ability to

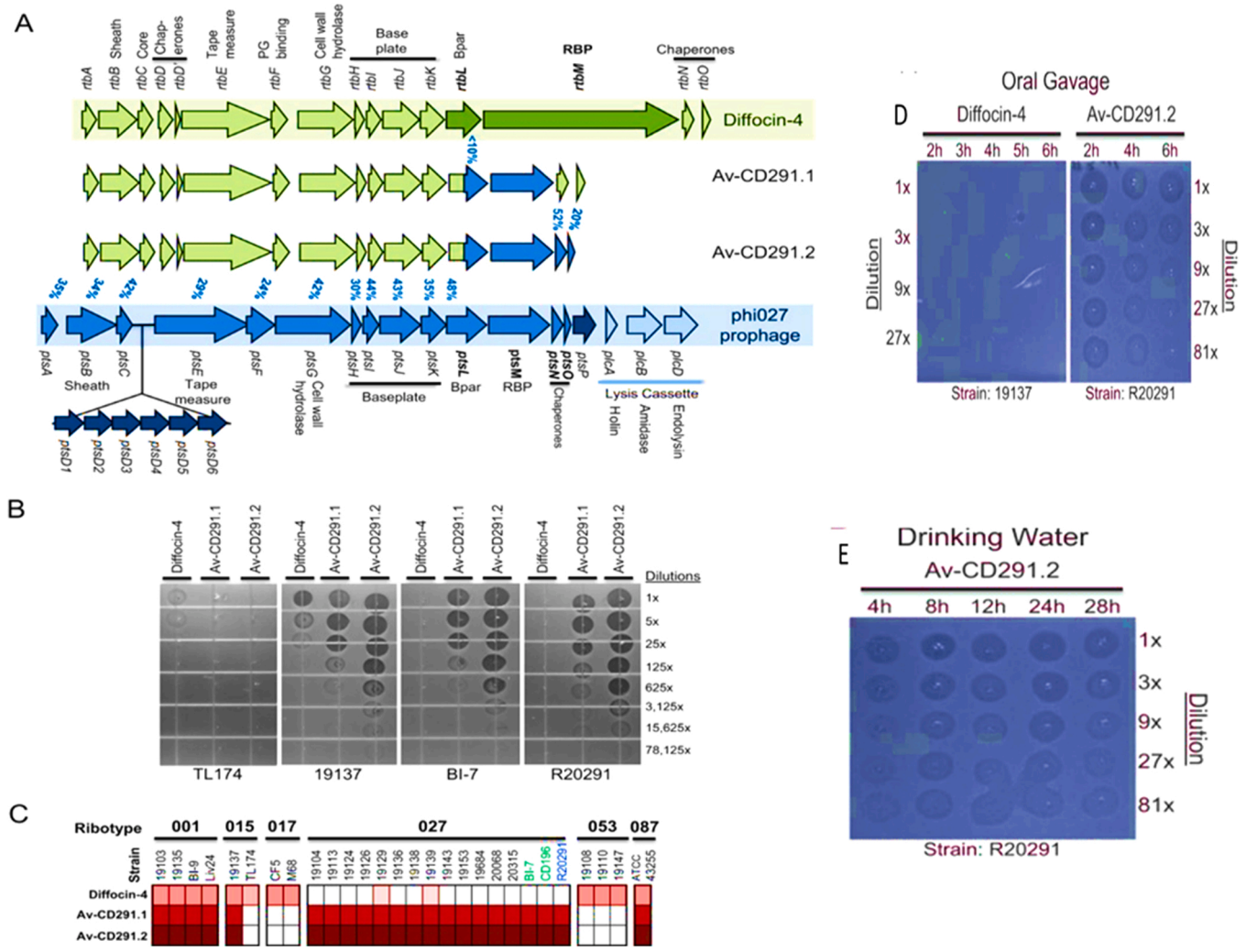

Fig. 10. : Influence of Phage tail like bacteriocins to combat *C. difficile* infections. (A) Retargeting diffocins with a prophage RBP from *C. difficile* strain R20291. (A) Schematic representation of gene clusters coding for diffocin-4 (green) and modified diffocins Av-CD291.1 and Av-CD291.2 and including the tail structure genes of the phi027 prophage (blue). For the phi027 prophage, the lysis cassette present only in the phi027 prophage is depicted in light blue and structural genes with no homology in the diffocin gene cluster are depicted in dark blue. The percentages of similarity between the diffocin-4 and phi027 genes are given (blue). (B) *In vitro* spot bioassays for bactericidal activity are shown for several strains. Preparations of diffocin-4, Av-CD291.1, and Av-CD291.2 were serially diluted and spotted on a soft agar lawn containing the indicated target strain. Dark zones of clearance indicate killing. Overlapping but distinct killing specificities for each diffocin preparation, which were all produced from a genetically identical *B. subtilis* host cell and by the same method, indicate killing is specific to diffocin and not due to any non-specific, contaminating *B. subtilis* protein. (C) The strain coverage for diffocin-4, Av-CD291.1, and Av-CD291.2 for ribotypes 001, 015, 017, 027, 053, and 087 is shown. White indicates no killing, and maroon indicates killing—with intensity of maroon reflecting robustness of killing. (D) Enteric pharmacokinetics of diffocin-4 and Av-CD291.2 orally administered to mice. R-type bacteriocins that survive transit through the GI tract intact are detectable in faeces by in vitro spot bioassays for bactericidal activity. Three groups of mice were administered diffocins in oral gavage and (E) drinking water.
(a) Genes are color coded according to source. (b) Adapted with open access permission from [56].

manufacture the R-type pyocin, which co-existed without killing each other [28]. The lysis of *P. aeruginosa* is caused by the induction of R-type and F-type pyocin for the formation of biofilms and membrane vesicles. The release of extracellular DNA is the most important factor in the formation of the biofilm matrix during this event [87]. However, when competing strains exist, the formation of an extracellular matrix as well as the killing of neighboring bacteria provides a double selective advantage [88].

Another intriguing biological study of a PTLB was conducted using *Xenorhabdicin nematophila* R-type *xenorhabdicin* [89]. This bacterium forms a symbiotic association with a nematode that infects the gut of insects. *Photorhabdus luminescens* acts as a competitor to *X. nematophilia*, and possesses the ability to suppress nematode growth. The production of xenorhabdicin, as R-type bacteriocin PTLB, was required for *X. nematophilia* to gain a competitive advantage over *P. luminescens* [88]. *Xenorhabdicin* gives a competitive and biological advantage for growth in the insect host. A P2-like tail synthesis gene cluster xnp1 was identified as essential for bacteriocin production via Mitomycin C. When any of the sheath or fiber genes are deleted, it caused the elimination of the production of this bacteriocin [90]. The hemolymph of insects was infected with *X. nematophilia* wild type, producing the bacteriocin but not the insects which were infected with an attenuated strain. *Xenorhabdicin* prepared from the wild-type strain killed the competitor bacteria *P.luminescens* sensitive to the bacteriocin. The elimination of this competitive bacteria took place in co-culture with *X.nematophila* wild type but not with the deletion strain. Thus, the bacteriocin possesses intra-species activity as it killed *X. nematophila* from *S. anatoliense* and a similar competitive advantage was provided by R-type PTLB from *X. bovienii*[88].

R-type PTLB is produced from bacteria *Rhizobium lupine* adsorbs or attaches to the surface of strain-growing cells [8]. A strain of bacteria produced bacteriocin causing inhibition of closely related strain through

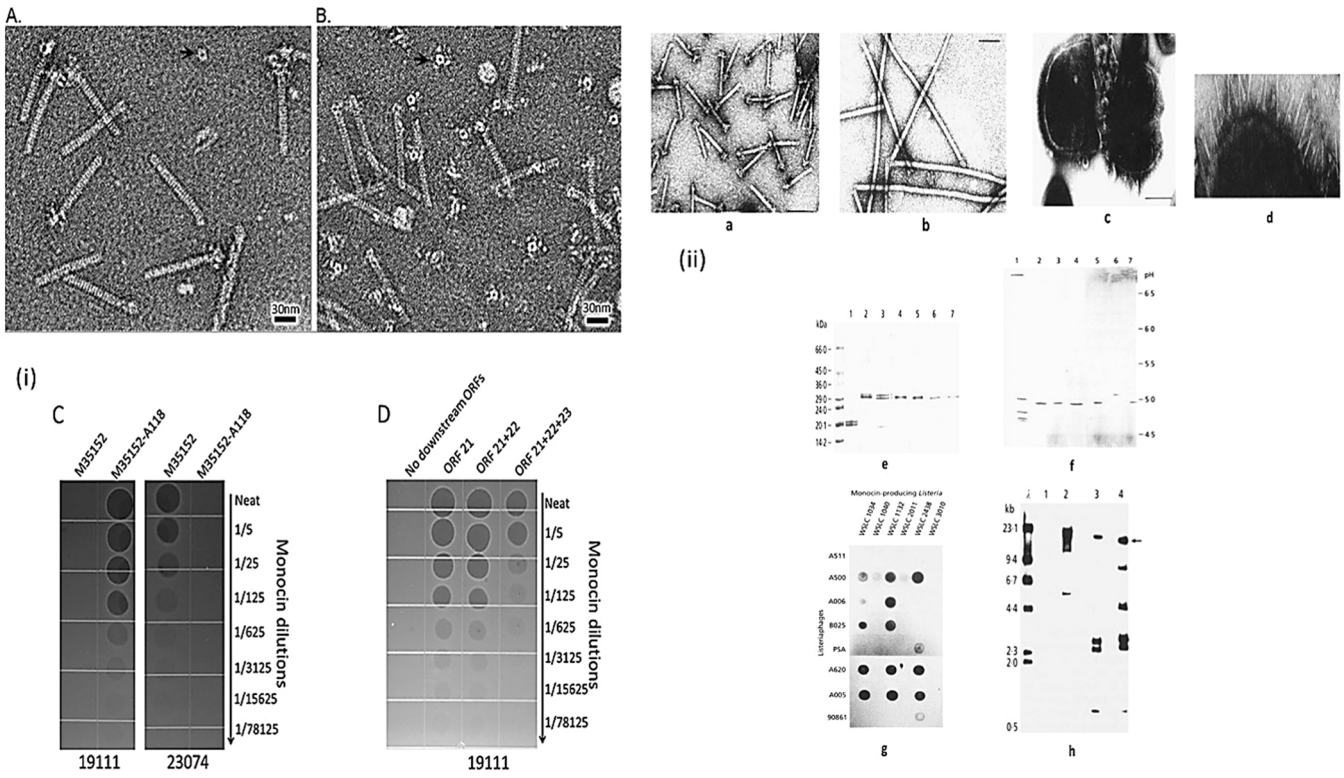

Fig. 11. Influence of Phage tail like bacteriocins to combat *L. monocytogenes* infections. (i) Transmission electron microscope images of monocin in (A, B). (C-D) explains the bacteriocidal activity of monocin to combat *L. monocytogenes.* Adapted with open access permission from. (ii)(a) Monocin M1040; bar, 100 nm. (b) Rod-shaped structures observed in some monocin preparations (M2011); bar, 100 nm. (c) *Listeria* cell (WSLC 3009) lysed by monocin M1040 after 30 min incubation: cell wall is severely destructed; bar, 500 nm. (d) Enlarged section of the cell surface with monocin particles attached; bar, 100 nm. (e-g) Electrophoretic analyses of monocin proteins via SDS-PAGE protein profiles and isoelectric focusing in immobilized pH gradients.
(a) Adapted with Open access permission from [22].

INCO particles as they do not possess ahead and cannot self-propagate. As bacteriocin particles attached to target cells, these particles possess a core surrounded by a contractile sheath with contracted and uncontracted structures [91]. In the uncontracted structure, a baseplate possessing spikes was attached to one end of the sheath whereas an end piece was seen protruding from the sheath of the periphery. In the contracted structure, the sheath contraction was responsible for the protrusion of the core and the baseplate was found attached to the contracted sheath via six tail fibers [92]. These fibers are responsible for the attachment of the baseplate of an adsorbing particle to the cell surface. As the INCO cores are presumably empty, adsorption of the particles to the bacterial surface causes contraction of the sheath. This exposes the core to contact with the cell wall leading to inhibition of the sensitive cells irreversibly to cell death [93].

8. Challenges and perspective

Phage tail-like bacteriocin (PTLBs) or tailocins are widespread among bacteria and are considered to be the strong protein nano-machines made by the bacteria [8]. Various engineering efforts have been elucidated to highlight their role in manipulating eukaryotic cells for precision warfare in bacterial species [94,95]. Further understanding of the molecular biology of tailocins structure and targeted mechanism will reveal a lot of unanswered questions about the release of tailocins in the environment by the bacterium and the reasons for targeting only specific strains of bacteria [96].

The potential of bacteriocins as a smart anti-bacterial agent is capable for diagnostic application through precision targeting against AMR pathogens and are the subjects to be investigated [97]. Future research and clinical trials focused on precision anti-bacterial are required to compartmentalize PTLBs as they as ideal nanomachines for targeted mitigation of MDR and XDR pathogens [98]. The efficacy of AvR2-V10.3 exhibits its antimicrobial potency against *E. coli* O157:H7 serotype of EHEC, thereby reducing the infection of enteric pathogens. Therefore, to serve the purpose of killing other serotypes, there is a requirement to develop highly specifically targeted pyocins against the other EHEC serotypes [50,99]. Further research focuses on the study of pharmacokinetics and pharmacodynamics properties of orogastric administered pyocins for the improvement of oral formulation and delivery methods (Fig. 12). Apart from this, studies can be oriented to the emerging AMR due to the introduction of new antibacterial agents like nanomaterials and polymeric materials intended to build antibiotics [100–102]. Furthermore, the prophylactic use of specifically targeted

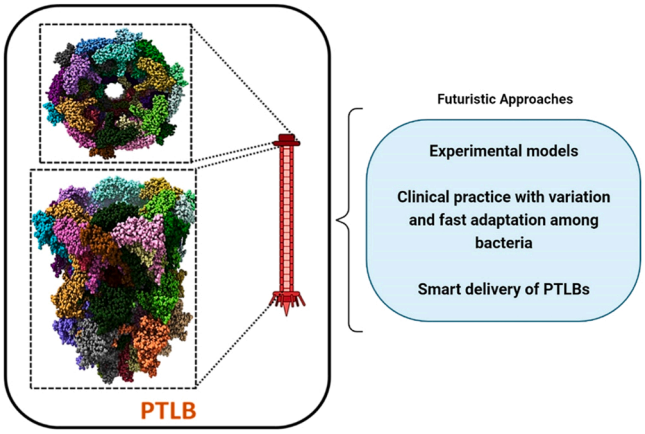

Fig. 12. Futuristic Approaches for biomedical applications of PTLBs.

bactericidal diffocins has gained popularity as an alternative therapy to CDI. The effectiveness of oral and parenteral R-type bacteriocins as therapeutics in animal models paves the way for the use of orally administered diffocins to prevent CDI. Due to the prevalence of more bacterial isolates, the major challenge is the production of a comprehensive set of diffocins using genetic engineering. Moreover, regulatory issues focusing on the large-scale productions of the PTLBs needs to be considered [3]. In the case of *Listeria* species, *lma* locus is considered to be widespread and conferred to play a role in pathogenesis [85]. The deletion of *lmaB* and *lmaD* in the mouse model resulted in lowered virulence however the mechanism remained unclear. More research is needed to effectively examine the mechanism and pathogenic functions of monocin production by *L. monocytogenes* before inculcation of their application in clinical settings [85].

9. Conclusion and outlook

This review presented some recent insights on the classification of phage-tail-like bacteriocins (PTLBs), their structure and mode of action, applications in combating severe infectious diseases, and recent advancements in the engineering of PTLBs against several antimicrobial resistance pathogens. PTLBs remains a hot topic of research due to the many possible application and further research focusing on the application of PTLBs in clinical trials needs to be addressed. The regulatory issues of large-scale productions of PTLBs and research focused primarily on those regulatory issues need to be done. When it comes to specificity, the receptor binding capacity of PTLB for targeting to the host receptor is the most pivotal factor. The interplay between receptor-binding domain targets and bacterial cell surface receptors is quite complicated. Antibacterial targeting specific bacteria are in high demand, therefore a correlation between phage tail-like particle genes and host bacterial receptors will bring close to AMR pathogen regression. Existing bacteriocin strains could be improved by molecular engineering, and new strains with unique features can be sought out to increase effectiveness and broaden uses. For increased effectiveness and utility in clinical setting of PTLBs integration with viral and non-viral vector could be approach.

CRediT authorship contribution statement

Rahul Bhattacharjee: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft. **Aditya Nandi:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft. **Adrija Sinha:** Methodology, Formal analysis, Investigation, Resources, Writing – review & editing. **Hrithik Kumar:** Methodology, Formal analysis, Investigation, Validation. **Disha Mitra:** Methodology, Formal analysis, Investigation, Validation. **Abhik Mojumdar:** Methodology, Formal analysis, Investigation, Validation. **Paritosh Patel:** Methodology, Formal analysis, Investigation, Validation. **Ealisha Jha:** Methodology, Formal analysis, Investigation, Resources, Writing – review & editing. **Suman Mishra:** Methodology, Investigation, Formal analysis, Software, Validation. **Prabhat Kumar Rout:** Formal analysis, Investigation, Resources, Writing – review & editing. **Pritam Kumar Panda:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – review & editing. **Suresh K. Verma:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Mrutyunjay Suar:** Conceptualization, Methodology, Software, Validation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflict of interest

There is no conflict of interest.

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