Abstract: Antimicrobial resistance (AMR) has become a global public health issue and antibiotic agents have lagged behind the rise in bacterial resistance. We are searching for a new method to combat AMR and phages are viruses that can effectively fight bacterial infections, which have renewed interest as antibiotic alternatives with their specificity. Large phage products have been produced in recent years to fight AMR. Using the “one health” approach, this review summarizes the phage products used in plant, food, animal, and human health. In addition, the advantages and disadvantages and future perspectives for the development of phage therapy as an antibiotic alternative to combat AMR are also discussed in this review.

Keywords: antimicrobial resistance; phage products; advantages and disadvantages of phage therapy; development prospects

1. Introduction

Antimicrobial resistance is a naturally evolving phenomenon that emerged soon after the discovery of penicillin in 1940 [1]. Antibiotics are highly efficient against bacterial infections, saving millions of lives and drastically reducing mortality rates. However, multidrug-resistant bacteria (MDR), extensively drug-resistant bacteria (XDR), and even pan-resistant bacteria (PDR) have evolved as a result of antibiotic overuse, abuse, and misuse. In particular, ESKAPE bacteria seriously threaten human health worldwide. According to the latest estimates, approximately 700,000 people worldwide die directly from AMR bacteria each year, with that number possibly rising to 1 billion by 2050 [2]. AMR is one of the top ten global public health threats facing humans, according to the WHO. As a result, FAO, WOAH, and WHO attach great importance to this and jointly launched the “one health” approach to combat AMR [3]. The interdependent relationship between the food chain and the environment makes resistant bacteria widespread in plants, animals, food, and humans, and the “one health” approach trinity model is ideally suited to address AMR [4,5]. Phages are currently one of the antibiotic alternatives with the most potential because of their ability to effectively combat bacterial infections. Phages are a new alternative therapy under the “one health” approach that can be used to control bacteria in plants, animals, food, and humans [6]. Currently, phage therapy is emerging globally, and in this review, we summarize the application of phage products for plants, animals, food, and human health from the perspective of “one health” from the two databases of phage companies and bacteriophage news [7,8]. Furthermore, the advantages and disadvantages
of phages as antibiotic alternatives to combat AMR and their future development prospects are also discussed in detail.

2. Phage Biology

As early as 1896, Ernest Hankin discovered antibacterial substances against *Vibrio cholerae* from water extracted from the Ganges and Jumna rivers in India, laying the foundation for the subsequent discovery of phages [9,10]. The term “phage” was introduced by Félix d’Herelle after he discovered the “anti-microbe” *Shigella* in 1917 [11]. Phages are abundant entities on the planet, with a population of $10^{31}$, which is 10–100 times that of their obligatory parasitic host bacterium [12]. The genome of phages is composed of single-stranded (ss) or double-stranded (ds) DNA or RNA, which is encapsulated by a wide variety of protein capsids. The universal viral taxonomy established by the International Committee on Taxonomy of Viruses (ICTV) divides phages into polyhedral, filamentous, pleomorphic, and tailed according to capsid morphology [13]. Phages can be classified into temperate and virulent based on their life cycle and reproductive characteristics. However, the process of bacterial infection is different between temperate and virulent phages.

Virulent phages enter the lytic cycle, which usually consists of five stages. The tail filament first adsorbs to a specific receptor on the surface of the host bacteria. These receptors can be located on cell walls, capsular polysaccharides, outer membrane proteins, efflux pumps, or appendages, such as pili and flagella [11] (Figure 1A). Second, the phage-derived enzymes (such as endolysins) lyse the peptidoglycan of the cell wall and the tail pipe penetrates through the cell membrane to inject its DNA into the host bacteria [14]. Third, phages perform biosynthesis, such as nucleic acid replication, RNA transcription, and protein translation in dormant cells. Fourth, phages assemble into progeny phages. Finally, when the number of progeny phages reaches a certain threshold, bacteria lyse and release progeny phages [15] (Figure 1B). For Gram-negative bacteria, lysis is achieved by three different functional proteins, holins, endolysins, and spanins, which act on the inner membrane, peptidoglycan, and outer membranes of the cell envelope, respectively [16]. Temperate phages differ from virulent phages in a number of important ways. For example, temperate phages integrate their genomes into the chromosomes of host bacteria, which do not lyse but enter the lysogenic cycle. Phages grow and multiply with host bacteria [17]. Under certain conditions, temperate phages can also enter the lytic cycle, depending mainly on phage-encoded repressors and regulators, as well as the control of phage enzymes [18]. For example, under stress responses and light, temperate phages can initiate the expression of lytic genes. Temperate phages can regulate the gene expression and behavior of bacteria through different mechanisms and enhance phage-host fitness [19]. In addition, both virulent and temperate phages have a pseudo-lysogenic nature, which means that viral DNA is present in the host bacteria in a form similar to a plasmid and the host at this moment is only the vector of the phage [14,18].

The key to killing bacteria by phages depends on lysing the bacterial cell wall and virulent phages are generally selected for treatment. It has commonly been assumed that icosahedral DS DNA phages containing tails can effectively treat human and animal infections [20]. Bacteria may acquire resistance genes or genes with pathogenic potential after the lysogenic transformation of temperate phages and they are generally not recommended for therapeutic purposes [11]. However, with advances in synthetic biology, temperate phages can be designed to interfere with bacterial intracellular processes and cause bacterial cell death. Alternatively, genomes of temperate phages were engineered to eliminate known virulence genes involved in the lysogenic cycle [21]. The current crisis of AMR makes phage therapy re-emerge globally and the cases of phage therapy in preclinical research are also gradually increasing [22–24].
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United States Environmental Protection Agency (USEPA) has approved several phage products to fight plant pathogens, and commercial phage products are summarized in Table 1. Only six phage products for plant health have been commercialized, mostly for soft rot Enterobacteriacea, Clavibacter michiganensis,
**Table 1. Commercial phage products for plant health.**

| Target Bacteria       | Company                        | Products          | Regulatory Approval | Certifications                        | Application                                                   | Ref.       |
|----------------------|--------------------------------|-------------------|---------------------|---------------------------------------|---------------------------------------------------------------|-----------|
| Soft rot Enterobacteriaceae | APS Biocontrol Ltd. (SCO)       | Biolyse® BP       | Approved            | UK, European                         | Food processing assistants in the potato packaging industry   | [34]      |
| Clavibacter michiganensis | OmniLytics Inc. (USA)           | AgriPhage CMM™    | EPA approved        | USA, Canada                          | Tomato bacterial canker                                        | [35,36]  |
| Xanthomonas citri     | Erwiphage PLUS (HU)             | Erwiphage         | Undefined           | Hungary                               | Fire blight caused by plants in the rose family               | [37]      |
| Variety of bacteria   | Fixed-Phage (UK)                | agriPHIX™         |                     | UK                                    | Effective improvement of storage for a range of crops         | [38]      |

4. Phage Products in Animal Health

The indiscriminate and extensive use of antibiotics in animals has been one of the principal reasons for the rapid spread of AMR. The new EU law prohibiting the prophylactic use of antibiotics in farmed animals was implemented in 2022 and the use of antibiotics is also strictly regulated in the United States and Canada [39]. The recent resurgence of phage therapy has also prompted the extensive application of phages in veterinary medicine. The first known therapeutic use of phages in veterinary medicine was associated with Felix d’Herelle, who used phages in 1919 to prevent and treat Salmonella infections in chickens and effectively reduce mortality in chickens [40]. However, when Pyle used phage therapy in 1926 to treat Salmonella Enteritidis infection in chickens, the results were less than encouraging [41]. Until the 1980s, William Smith reconsidered the use of phage therapy in animals and experimented with chickens, cattle, and pigs [42]. The early British team conducted a small clinical trial of a phage cocktail for canine otitis media caused by P. aeruginosa in 2010 and the results were greatly encouraging [43]. Subsequently, the application of phages in animals has been increasing, mainly for treating E. coli and Salmonella infections in poultry and pigs, as well as mastitis in cattle caused by S. aureus [44]. In aquaculture, phages are also effective against Vibrio, Pseudomonas, and Aeromonas, reducing fish mortality [45].

The preharvest application of phages can effectively reduce the infection and colonization of live poultry and minimize the risk of pathogens entering the food chain, thereby reducing the infection of zoonotic bacteria [46]. At present, phage products in animals mainly focus on the preharvest application of livestock, poultry, and the clinical application of pets. The detailed commercial phage products used in animals are shown in Table 2. A total of 9 of the 38 veterinary phage products counted have been approved by the FDA and 3 by the European EFSA. The products developed by Intralytix (Baltimore,
AR, USA) mainly focus on pet food safety and preharvest intervention. The product line of PhagePharm (Qingdao, China) focuses on common pathogens in the environment and is used as an environmental improver, and the product line of Fixed-Phage (UK) is mostly phage cocktails. Figure 2A reveals that 20 mono-component phage products in the market almost target *E. coli*, *Salmonella*, and *C. perfringens* in poultry. A variety of phage cocktail products also target the infection of these bacteria. Most veterinary phage products are mainly in the form of food additives in animal feed or drinking water to prevent and control bacterial diseases. Only a few phage products are made into gel formulations for topical epidermic medication, such as Staphage Lysate (SPL)®, a phage product from Delmont Laboratories (Swarthmore, PA, USA), which is also the only staphylococcal product approved for use in *Staphylococcus* canis skin infections [47]. In contrast, phage products targeting companion animals remain to be further investigated, especially the study of bacterial dermatology, which may have significance in the future.

![Figure 2](image-url)

**Figure 2.** Analysis of phage products from the perspective of the “one health” approach. (A) Targeted bacteria for mono-component phage products in animals. (B) Targeted bacteria for phage products in food processing. (C) Targeted bacteria for mono-component phage products in humans. (D) Main dosage forms of phage products in human therapy. (E) Main routes of administration for human phage products.
| Target Bacteria          | Company                                      | Products                                 | Regulatory Approval | Certifications          | Application                                                                 | Ref. |
|-------------------------|----------------------------------------------|------------------------------------------|---------------------|-------------------------|-----------------------------------------------------------------------------|------|
| **E. coli**              | Intralytix (USA)                             | Ecolicide®                               | FDA                 | USA                     | For *E. coli O157:H7* contamination in Pet Food                             | [48] |
|                         |                                              | Ecolicide PX™                            |                     |                         | For *E. coli O157:H7* contamination on animal fur                          |      |
|                         | Arm and Hammer Animal & Food Production (USA)| Finalyse®                                | USDA, FSIS          | USA                     | A preharvest antimicrobial hide wash used to reduce *E. coli O157:H7*      | [34] |
|                         | Proteon Pharmaceuticals (POL)                | BAFACOL™                                 | EFSA                | Poland                  | Feed additive to prevent pathogenic *E. coli* in poultry.                   | [49] |
|                         | Phagelab (CHI)                              | Swine product                            | Undefined           | Chile                   | Liquid Food Additive Eliminates *E. coli* in Swine                         | [50] |
| **Salmonella**           | Intralytix (USA)                             | SalmoLyse®                               | FDA                 | USA                     | *Salmonella* Contamination in Pet Food                                      | [51,52]|
|                         |                                              | PLSV-1™                                  |                     |                         | *Salmonella* Contamination in Poultry                                       | [44,53]|
|                         | UniFAHS                                      | SalmoGuard                               | FDA                 | Southeast Asian countries| Poultry feed additives                                                      | [51,54]|
|                         | OmniLytics Inc. (USA)                       | BacWash™                                 | USDA                | USA                     | For Hides of livestock surface disinfection                                 | [56] |
|                         | SciPhage (CO)                               | SalmoFree®                               | Undefined           | Colombia                | Feed additive for control of *Salmonella* infection in poultry              | [57] |
|                         | PhagePharm (CHN)                            | NuoAnSha                                 | Approved            | China                   | Improve the breeding environment                                            | [58] |
|                         | Phagelab (CHI)                              | Poultry product                          | Undefined           | Chile                   | Liquid food additive to eliminate *Salmonella* in broilers.                 | [50] |
| **L. monocytogenes**     | Intralytix (USA)                             | ListPhage®                               | FDA                 | USA                     | *L. monocytogenes* in pet food                                              | [48] |
|                         |                                              | INT-401™                                 | FDA, FSIS           |                         | Against Poultry *C. perfringens*                                            | [59] |
| **C. perfringens**       | PhagePharm (CHN)                            | NuoAnSuoQing                             | Approved            | China                   | Necrotizing enteritis, diarrhea, intestinal bleeding caused by *C. perfringens* | [58] |
| **staphylococcus**       | Delmont Laboratories (USA)                  | Staphage Lysate(SPL)®                    | FDA                 | USA                     | *Staphylococcal* skin infections in dogs                                    | [47] |
| **Yersinia ruckeri**     | ACD Pharma (NOR)                            | CUSTUS® YRS                              | FOT                 | Norwegian               | Various bacteria in aquaculture farms                                      | [60] |
| **R. anatipestfer**      | PhagePharm (CHN)                            | JiangYanQing                              | Approved            | China                   | Decontamination of *R. anatipestifer* in aquaculture environments           | [58] |
| **Weisella ceti**        | SciPhage (CO)                               | Weissella Ceti Phages                    | Undefined           | Colombia                | control *weissellosis* in trout                                            | [61] |
### Table 2. Cont.

| Target Bacteria | Company | Products | Regulatory Approval | Certifications | Application | Ref. |
|-----------------|---------|----------|---------------------|----------------|-------------|------|
| Variety of bacteria | | | | | | |
| | CJ Cheiljedang Research Institute of Biotechnology (KOR) | Biotector® | Undefined | South Korea | Feed additive for poultry and pigs against *Salmonella*, *C. perfringens*, *E. coli*. | [35] |
| | Phagelab (CHI) cattle product | undefined | undefined | undefined | Food additive prevent infectious diarrhea caused by *E. coli* and *Salmonella*. | [50] |
| | Proteon Pharmaceuticals (POL) | BAFADOR® | EFSA | Poland | Fish feed additive against *Aeromonas* and *Pseudomonas* | [62] |
| | PhagePharm (CHN) NuoAnQing YaLiNing | Approved | China | Improve the breeding environment | | [58] |
| | Varmsphage (CHN) ChangShi | | | | Infections caused by *E. coli* and *Salmonella* | [63] |
| | Cytophage (CAN) Poultry Feed Additives | undefined | Canada | Prevents the common bacterial infections in chickens | | [64] |
| | Fixed-Phage (UK) | | Approved | UK | Feed additives | [37,49] |
| | Pathway Intermediates (KOR) ProBe-Bac | FDA | South Korea | ProBe-Bac SE for pigs; ProBe-Bac PE for poultry | | [65] |
| | Phagelux (CHN) | LUNIN LUZON LUMON | Approved | China | for poultry diseases | for swine disease | for cattle disease | |
| | MicroMir (RUS) | Vetagin® | Approved | Russia | Prevention of bacterial endometritis, abscess and myositis in dairy cows | Control of common bacteria associated with lower respiratory tract disease | |
| | | Bronchophage | Approved | Russia | | | |
| | | Phagovet | | | | |

5. Phages Products in Food Health

The use of antibiotics aggravates AMR in livestock and poultry products and the high morbidity and mortality caused by foodborne pathogens has been a global burden [68]. Contamination caused by foodborne pathogens can be transmitted from production lines to humans, ultimately threatening human health. Phages are desirable for the biological control of foodborne pathogens as an effective natural and ecological alternative [69]. There are also increasing studies on the effectiveness of phages against foodborne pathogens. For example, Mengzhe demonstrated that phage STP4-A with a wide host range is effective...
against Salmonella as a food additive [70]. Vikram demonstrated that phage preparation can effectively reduce the level and prevalence of E. coli O157:H7 in food [71]. As early as 1958, the U.S. Food and Drug Administration (FDA) recognized phages and their derivatives as GRAS (generally recognized as safe) through the Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act [72]. Phages are primarily used in three departments: primary production, biological preservation, and biological harmlessness in the food industry to ensure food safety [53]. Phages used in primary food production can prevent foodborne pathogens from entering the human body through the food chain, which is an excellent pre-harvest strategy. Livestock and poultry products are contaminated with pathogens in the production, processing, distribution, and consumption links. The application of phage products in postharvest can effectively reduce the presence of pathogens on carcasses, packaging, and RTE poultry products [68]. The benefit of phages for postharvest poultry processing is that they do not affect the quality senses and nutritional value of food [48].

Phage products are currently used with high safety to eliminate pathogens in animal food (meat products and dairy products) and plant food (fruits and vegetables). The FDA has granted phage products GRAS approval, allowing them to be used in livestock and poultry products. The use of phage products in food is also approved by health agencies in Israel, Canada, China, Switzerland, Australia, New Zealand, and the European Union [53]. Since the FDA approved the first phage product, ListShield™, as a food preservative in 2006, a significant number of phage products have emerged worldwide to combat foodborne pathogens [34,73]. As of November 2021, 14 phage products have been used in food processing, of which 11 have been approved by the FDA, including Intralytix (USA) and Micreos (Utrecht, Netherlands). Table 3 lists the commercial phage products used to combat foodborne pathogens in detail. The statistics of approved commercial phage products against foodborne pathogens revealed that Intralytix (USA) has made remarkable contributions to the field, with five products for marketing, and has gained Jewish cleansing and halal certification. Figure 2B reveals that commercial phage products primarily compete with E. coli, Salmonella, and L. monocytogenes, which seriously threaten human health. It is worth noting that Campylobacter is the most commonly reported foodborne pathogen, but there are no commercial Campylobacter phage products. A recent project (C-SNiper) directed by the Spanish Technology Center (AZTI) developed a prototype phage product for Campylobacter that is expected to be globally commercialized in 2022 [74].

Table 3. Commercial phage products fighting foodborne pathogens in food.

| Target Bacteria | Company | Phage Products | Regulatory Approval | Certifications | Application | Ref. |
|-----------------|---------|----------------|---------------------|----------------|-------------|------|
| E. coli         | Intralytix (USA) | EcoShield PX™ | FDA | Canada; Israel; USA | Eliminate E. coli O157:H7 contamination prior to grinding or packaging | [71,75] |
|                 | Micreos (NED) | PhageGuard E™ | USA | E. coli O157 on beef carcasses, primals, subs and trimmings. | [76] |
|                 | FINK TEC GmbH (GER) | Secure Shield E1 | FDA | | | |
| Salmonella      | Intralytix (USA) | SalmoFresh™ | USA, Canada, Israel | Food additives for poultry, fish, shellfish, fruits and vegetables. | [77] |
|                 | Micreos (NED) | PhageGuard S™ | Canada; Israel; Halal; OMRI; SKAL | In spray or dipping form for poultry, meat. | [78] |
|                 | Phagelux (CHN) | SalmoPro® | Canada, China | As an antibacterial processing aid in food. | [56] |
|                 | Arm and Hammer Animal & Food Production (USA) | Finalyse™SAL | Undefined | USA | For Salmonella in poultry products. | [79] |
Table 3. Cont.

| L. monocytogenes | Intralytix (USA) | ListShield™ Listex™ | USA | Food additives for poultry, fish, shellfish, fruits and vegetables. [80] |
|------------------|------------------|---------------------|-----|--------------------------------------------------------------------------------|
|                   | Micreos (NED)    | PhageGuard Listex™  | FDA | In spray or dipping form for poultry, meat. [81] |
| Campylobacter     | Intralytix (USA) | Compyshield™        | USA | Food additives for raw red meat [82] |
| Shigella          | Intralytix (USA) | ShigaShield™        | USA | Removal of Shigella from meat and vegetables [83] |
| Variety of bacteria | Brimrose Technology Corporation (USA) | EnkoPhagum | Approved | Salmonella, Shigella, E. coli, Staphylococcus in meat products. [53] |
|                   | Fixed-Phage (UK) | safePHIX™           | Undefined | UK | Against bacteria in the food cold chain [38] |

6. Phage Products in Human Health

The application of phages to treat human diseases dates back to the successful injection of phage preparations in France in 1921 to treat five children with dysentery caused by the Shigella infection [24]. Belgian researchers published the first paper in the same year on the successful use of phages to treat furuncles and carbuncles of human skin [9]. Initially, the French company L’Oréal sold five phage preparations for the treatment of bacterial infections, Antipiol (Deutsch, Germany) produced Enterofagos, and EliLily (Indianapolis, IN, USA) first sold “Staphylofel” phage preparations for the treatment of streptococci and E. coli [86]. D’Herelle and Eliava first used phages to control cholera in India in 1931 and found no side effects following treatment [87]. During World War II, phages were also applied by both Soviet and German armies to treat wound infections, with the German army using Shigella phage preparation “Polyfagin” by Behringwerke Leverkusen to treat and prevent dysentery in soldiers [88]. In the late 1930s, however, the Committee on Pharmacy and Chemistry of the American Medical Association stated that the efficacy of phage therapy was unclear and further research was needed. Together with the discovery of penicillin, which led to the successful introduction and widespread use of antibiotics, interest in phage therapy has diminished, with only the Soviet Union and some countries in Eastern Europe still investigating it [14].

Common infections or minor injuries may be fatal with the increasing threat of AMR to humans. Researchers found great potential for phage therapy and phage therapies are increasingly being used for human bacterial diseases. In 2000, clinical human trials using phage therapy as a potential antibiotic alternative officially began in the United States, and phase I clinical data was first published in 2009. Clinical trials have revealed that phage cocktails against E. coli, S. aureus, and P. aeruginosa are safe for the treatment of wounds [89]. In 2013, the European Commission supported the large multinational phage therapy multicenter clinical research program “Phagoburn”, which treated 27 patients infected with P. aeruginosa burn wounds with phage therapy in France, Belgium, and Switzerland [90]. Despite the intended purpose not being achieved, this is the first time that three national regulatory agencies reached a consensus about phage cocktails for human therapy. At present, there are five phage therapy institutions worldwide, which are: Eliava Phage Therapy Center (Tbilisi, Georgia), Phage Therapy Center (Tbilisi, Georgia), Center for Innovative Phage Applications and Therapeutics (West Philadelphia, PA, USA), Phage International (San Ramon, CA, USA), and Phage Therapy Unit (Wrocław, Poland). Eliava Phage Therapy, founded in 1923, was the first institution to focus on phage therapy and has marketed phage cocktail products targeting specific pathogenic bacteria to treat human bacterial infections [91].

It has been confirmed that phage therapy has a lethal impact on a range of bacteria, which has contributed to an increase in phage therapy research and development for
human diseases by multiple institutions around the world. However, no phage products have been approved for human use in the European Union or the United States. The FDA has merely opened up the regulatory pathway for phages to provide a green channel for phage products for clinical use in emergencies. Phage therapies are approved for use in emergency treatment plans in the European Union, Australia, France, and Belgium [92]. Detailed information on phage products currently approved and in preclinical studies worldwide is provided in Table 4. Figure 2C reveals that phages in preclinical products are almost exclusively targeted at MDR bacteria, especially “ESKPAEE” pathogens, including *E. faecium, S. aureus, K. pneumoniae, E. coli*, and others. It can treat the infections caused by these bacteria at different sites, including bone and joint infections (IOA), diabetic foot ulcers (UPD), and MARS caused by *S. aureus* [93,94]. It can treat the fibrosis and burn infections caused by *P. aeruginosa* [95]. It can treat urinary tract infections and IBD caused by *E.coli* and *K. pneumoniae* [96,97]. Among the preclinical phage products, the cocktail products composed of 4–8 phage mixtures account for 60% of the total.

Table 4. Phage products for human health.

| **Target Bacteria** | **Company** | **Product** | **Regulatory Approval** | **Route of Administration** | **Application** | **Ref.** |
|---------------------|-------------|-------------|-------------------------|----------------------------|----------------|---------|
| *E. coli*           | Intralytix  | EcoActive™  | FDA approved IND, Phase 1/2a oral | Targeting adherent-invasive *E. coli* | [98] |
|                     | Pherecydes Pharma (FRA) | PhagUTI | Phase I/II Undefined | Treating *E. coli* Urinary Tract Infections | [99] |
|                     | Phico Therapeutics (UK) | SASPject PT5 | Undefined Intravenous injection | Fights diseases caused by *E. coli* | [100] |
| *P. aeruginosa*     | Microgen (RUS) | Bacteriophage *P. aeruginosa* Russian Federation national standard certification Oral intrarectal, or Intracavitary injection | Treatment and prevention of diseases caused by *P. aeruginosa* | [101] |
|                     | Armata (USA) | AP-PA02; AP-PA03 | FDA approved IND, Phase 1b/2 Inhalation | Treatment of respiratory tract infections caused by *P. aeruginosa*, especially in patients with CF | [95] |
|                     | BiomX (USA) | BX004 | Preclinical Oral | Spray and gel for burn care | [102] |
|                     | Phagelux (CHN) | PGX0100 | FDA approved IND, preclinical Transdermal | | [103] |
|                     | Phico Therapeutics (UK) | SASPject PT3 undefined | Undefined | Against *P. aeruginosa* infection | [104] |
|                     | Pherecydes Pharma (FRA) | Pneumo Phage | Phase I/II clinical trials are expected to start in 2023 Inhalation | Treatment of acute *P. aeruginosa* respiratory tract infection | [99] |
| Target Bacteria | Company | Product | Regulatory Approval | Route of Administration | Application | Ref. |
|-----------------|---------|---------|---------------------|-------------------------|-------------|------|
| Microorganisms  | Microgen (RUS) | Staphylococcal bacteriophage | Russian Federation national standard certification | Inhalation | Treatment of Suppurative Inflammation and Intestinal Disorders Caused by Staphylococci | [101] |
|                 | Armata (USA) | AP-SA01; AP-SA02 | FDA approved IND, Phase 1b/2 | Intravenous injection | Treatment of resistant and refractory Staphylococcus aureus bacteremia and diabetic foot ulcers | [93,94] |
|                 | BiomX (USA) | BX005 | Preclinical stage | | Atopic dermatitis caused by S. aureus | [102] |
|                 | Phagelux (CHN) | PL-01-SZ | China NMPA IND submission expected in 2022 | Transdermal | S. aureus lyase, a hydrogel formulation for the treatment of eczema | [103] |
| S. aureus       | Phagelux (CHN) | PL-06-FC | | | Pacnes and S. aureus lyase, hydrogel for acne treatment | |
|                 | iNODExWorld (KOR) | N-Rephasin® SAL200 | Phase II | Intravenous injection | Effective against MRSA | [105,106] |
|                 | Pherecydes Pharma (FRA) | Phage Cocktail | Phase I/II | Undefined | Fights bone and joint infections (JOA) and diabetic foot ulcers (DFU) caused by S. aureus. | [99] |
|                 | Phico Therapeutics (UK) | SASPject PT1.2 | Phase I | | Engineered phages deliver genes for antimicrobial proteins (SASPs) that rapidly kill S. aureus | [107] |
| Staphylococcal | Eliava Bio Preparation (GEO) | Staphylococcal Bacteriophage | Georgian Approval | Oral or intrarectal | Prevention and treatment of postoperative wound infections, Staphylococcal infections | [108] |
| K. pneumoniae   | BiomX (USA) | BX003 | Phase I | Oral | Targeting K. pneumoniae bacterial strains present in the gut of IBD and PSC patients | [102] |
| Shigella        | Intralytix (USA) | ShigActive™ | FDA approved IND, 2021 | Oral | Prevention of human diseases caused by Shigella infection | [109] |
| Enterococcus    | VRELysin™ | Undefined | Undefined | | Colonization with antibiotic-resistant Enterococci and associated bacteremia | [84] |
| C difficile     | AmpliPhi (UK) | AmpliPhage-004 | Pre-phase 1 | Undefined | Against C. difficile (including highly virulent RT027) | [104] |
### Table 4. Cont.

| Target Bacteria          | Company                  | Product                        | Regulatory Approval                          | Route of Administration | Application                                                                 | Ref. |
|--------------------------|--------------------------|--------------------------------|----------------------------------------------|-------------------------|-----------------------------------------------------------------------------|------|
| *Streptococcal*          | Microgen(RUS)            | Streptococcal bacteriophage    | Russian Federation national standard certification | Oral, topical and intrarectal | Treatment diseases caused by *Streptococcus*                                | [101]|
| *Gardnerella spp*        | BioNTech R&D(AUT)        | PM-477                         | Preclinical                                   | Undefined               | Recurrent bacterial vaginosis, synthetic lysosomes                           | [110]|
| *Fusobacterium nucleatum*| BiomX (USA) engineered phage | Preclinical                      | Intravenous injection                         |                         | Targeting *Fusobacterium nucleatum* bacteria present in the tumor micro environment | [111]|

#### Combining targets against variety of bacteria

| Dosage Form | Company                  | Product                     | Regulatory Approval                          | Route of administration | Application                                                                 | Ref. |
|-------------|--------------------------|-----------------------------|----------------------------------------------|-------------------------|-----------------------------------------------------------------------------|------|
| Phage spray | Phagyo® spray            | Septaphage® table           | Georgian Approved                            | Topical                 | Treatment and prophylaxis of bacterial purulent-inflammatory infections (multiple microorganisms) | [112]|
| Phage tablet| Septaphage®              | Phagyo®                     | Oral                                         |                         | For bacterial infections, indigestion                                         |      |
| Phage cocktail| Biochimpharm (GEO)    | Travelphag™                 | Oral, intrarectal                            |                         | Treatment and Prevention of Diseases Caused by *Salmonella*                  |      |
| Phage cocktail| Microgen (RUS)         | *Salmonella* groups A,B,C,D, bacteriophage | Oral, intrarectal                            |                         | Treatment and prevention of purulent inflammatory and enteric diseases, dysbacteriosis caused by bacteria Proteus and enterotoxigenic *E.coli* |      |
| Phage cocktail|                        | *E.coli*-Proteus bacteriophage | Oral, topical and intrarectal                |                         | Specific lysis of *K. pneumoniae, K. odorifera, K. rhinosclerosis.*          | [101]|
| Phage cocktail|                        | *Klebsiella* purified polyvalent bacteriophage | Oral, topical and intrarectal                |                         | Treatment and prevention of bacillary dysentery                              |      |
| Phage cocktail|                        | *Intesti-bacteriophage*      | Oral, topical and intrarectal                |                         | Treatment and prevention of purulent inflammation and intestinal diseases   |      |
| Phage cocktail|                        | Sextaphage® Polyvalent Pyobacteriophage | Oral and intrarectal                         |                         | Specific lysis of *Staphylococcus, Streptococcus, Enterococcus, Proteus, K.pneumoniae, P.aeruginosa and *E. coli.* |      |
| Phage cocktail|                        | Complex Pyobacteriophage     | Oral and intrarectal                         | Specific lysis of the bacillary dysentery pathogen |                                                                                                                                 |      |
| Phage cocktail|                        | Dysentery polyvalent bacteriophage | Oral and intrarectal                         | Specific lysis of the bacillary dysentery pathogen |                                                                                                                                 |      |
| Target Bacteria | Company | Product | Regulatory Approval | Route of Administration | Application | Ref. |
|----------------|---------|---------|---------------------|-------------------------|-------------|------|
| Phage cocktail | Eliava Bio Preparation (GEO) | Pyo-Phage | Georgian Approved | Oral, intrarectal, or intracavitary injection | Treatment and prevention of bacterial purulent inflammation and intestinal infections. | [113] |
|                 |         | Fersisi-Phage |                      | Oral or intrarectal, or intracavitary injection |                  |      |
|                 |         | Intesti-Phage |                      | Rectal, or intracavity injection |                  |      |
|                 |         | SES-phage |                      |                          |                  |      |
|                 |         | ENKO-Phage |                      |                          |                  |      |
| Phage spray | Bacteriophage Staphylococcus spray MediPhag | Topical(spray) | A mix of sterile lysate phages against S. aureus |                  |      |
| Phage cocktail | Aziya Immuno-preparat (UZ) | Bacteriophage Staphylococcus liquid MediPhag |                      |                  |                  |      |
|                 |         | Bacteriophage Salmonella polyvalent MediPhag | Marketed | Oral | Treatment and prevention of multiple serotypes of Salmonella | [114] |
|                 |         | Bacteriophage Dysenteric Polyvalent MediPhag |                      |                  |                  |      |
|                 |         | GastroFag polyvalent MediPhag |                      |                  |                  |      |
| Phage capsule | Bacteriophage dysenteric polyvalent “MediPhag” |                      |                  |                  |                  |      |
| phage tablet | MB Pharma (CZ) | LYZODOL® | Marketed | Oral | Against S.aureus, K.pneumoniae, Lelliottia amnigena, Propionibacterium acnes causing respiratory infections. | [115] |
| Phage gel | MicroMir (RUS) | Phagodent |                      | Contains 72 phage complexes to normalize oral microflora |                  |      |
|            |         | Phagoderm |                      | Skin gel containing 64 phages to prevent bacterial infection of the skin. |                  |      |
|            |         | Phagogyn | Marketed | Topical | Gel containing 74 phages that prevent bacterial diseases of the reproductive system. | [76] |
|            |         | Otophagus |                      | Gel containing 69 phages that prevent bacterial and suppurative inflammation of the ear, nose and throat |                  |      |
**Table 4. Cont.**

| Target Bacteria | Company | Product | Regulatory Approval | Route of Administration | Application | Ref. |
|-----------------|---------|---------|---------------------|-------------------------|-------------|------|
| **Phage cocktail** | Phagex (UKR) | Phagex (UKR) | Marketed | Oral and topical | Treatment of pathogenic factors in purulent inflammation and intestinal diseases caused by *Streptococcus pyogenes*, *S. aureus*, *E. coli*, *P. aeruginosa*, *Proteus vulgaris*, *Proteus mirabilis* | [116] |
| | Intestifag<sup>®</sup> polyvalent bacteriophage | | | | Fights intestinal diseases caused by *Shigella*, *Salmonella*, *E. coli*, *P. aeruginosa*, *Enterococcus faecalis*, *S. aureus* | |
| | Phico Therapeutics (UK) | SASPject PT4 | Undefined | Intravenous injection | Treatment and prevention of diseases caused by *K. pneumoniae* and *E. coli* | [100] |
| | Phagelux (CHN) | BACTELIDE™ | FDA approved IND, preclinical | Transdermal | Patches and sprays for pressure ulcers | [103] |
| | Fixed-Phage (UK) | mediPHIX™ | Undefined | Undefined | Effective against a variety of bacteria | [38] |
| | Adaptive Phage Therapeutics (USA) | PhageBank | FDA approved IND, Phase 1/2 | Intravenous injection | Treat Diabetic Foot Osteomyelitis, Prosthetic Joint Infection, Chronic Recurrent UTI, Ophthalmic Infection, Cystic Fibrosis-related Lung Infection | [117] |
| | Locus Biosciences (KOR) | crPhage™ | Phase 1b | Injection | Combined with CRISPR-Cas3 to enhance bactericidal efficacy against various bacterial diseases such as IBD and UTI | [118] |
| | Ellis Day Skin Science (USA) | Balancing Phage Serum | Marketed | | Eliminate bacteria associated with blemishes and acne to balance the skin microbiome | [119] |
| | | Hydrating Phage Serum | Marketed | Transdermal | | |
| | PHYLA (USA) | Phortify Probiotic Serum | Marketed | | A probiotic serum that targets and neutralizes acne-causing bacteria | [120] |
| | SciPhage (CO) | AcneFree | Undefined | | Fights acne-targeting bacteria | [61] |

Phage cocktails can increase the host range and avoid targeting a specific pathogen. In addition, rapid identification of bacterial pathogens is a time-consuming and laborious process before individualized treatment with phages [121]. Notably, phage cocktails are still targets for treating bacterial diseases caused by “ESKPAEE” pathogens. Figure 2D
reveals that phage cocktail products that have been marketed in Russia and Georgia are also basically liquid phage cocktails, with only a few gels, capsules, and tablets available. Due to the effective identification of phages in the reticuloendothelial system, the half-life of phages in humans is usually relatively short [122]. Figure 2E reveals that the route of administration has a significant impact on the efficacy of phage absorption into the human body. Currently, the administration routes of phage products in preclinical studies mainly include oral, topical, transdermal, inhalation, and intrarectal administration. There are various routes of administration for phage products, with oral administration accounting for 35% of the total and remaining the most prevalent, followed by topical and intrarectal administration. Oral administration is effective in delivering phages to the gastrointestinal tract but it is the least effective route for systemic penetration. The most effective mode of delivery is an injection, which may deliver phages to practically all organs and tissues in minutes. Therefore, the efficacy of phage therapy is determined by the route of administration.

Endolysin and virosome-associated lysozyme (VAL), which are phage-derived peptidoglycan-degrading enzymes, are also bactericidal. Endolysins are enzymes used by phages to lyse the bacterial cell wall at the end of the replication cycle, while the VAL is responsible for the injection of genetic material into infected cells for peptidoglycan degradation [18,123]. Many studies on the antibacterial effect of endolysin are currently being implemented in human medicine clinics. Endolysin is also one of the alternatives to antibiotics. It has the advantages of killing the host quickly, host specificity, preservation of the normal microbial community, reduction of AMR risk, and efficiency against multidrug-resistant bacteria and biofilms when compared to antibiotics [124]. The benefits of endolysin therapy have attracted the attention of researchers and pharmaceutical companies to its commercial potential and several commercial products based on endolysin have now been developed. The first human endolysin product developed by Micreos, Staphefekt SA. 100, specifically for the treatment of chronic S. aureus associated skin diseases, has been marketed. All three clinical patients had a positive therapeutic effect and did not develop resistance [125]. Artilysin has developed an Artilysin® product line (Lysando AG, Regensburg, Germany) that is effective against resistant P. aeruginosa and A. baumannii in various forms including spray, nebulizer, solution, lyophilization, gel, and coating [126]. Rephasin® SAL200 (Intron Biotechnology, Seongnam, Korea) is now in phase II of human clinical trials [105,127]. ContraFect has developed a novel direct lysing agent called Amurin peptide, which is effective against numerous Gram-negative pathogens. The other is a lysin-based direct lytic agent, containing Exebacase CF301, which is effective against S. aureus, including MARS, and is the first phage lytic enzyme to enter human clinical trials in the United States [128,129]. Criteria used for the preclinical analysis of small molecule antibiotics may be more readily translated into the preclinical assessment of phage lytic enzymes than phages, so clinical evaluation of phage lytic enzymes is progressing significantly faster [130].

7. Advantages and Disadvantages of Phage Therapy

Compared to antibiotics, phages are characterized by host specificity, which means only lysing the host bacterial cell wall without destroying the microbiota [62]. There is a process of adaptation versus counter-adaptation in the coevolution of phages and bacterial hosts and the risk of developing resistance is low [40]. For example, coevolutionary phage training can delay the evolution of phage resistance. Researchers conducted coevolution experiments using E. coli and untrained or trained phages to assess the potential of phage-training treatments and found that trained phages were able to inhibit host bacteria for a longer period of time [131]. The coevolution of phages with host bacteria has also driven bacteria to evolve a variety of highly specific phage defense mechanisms. For example, mutations in phage receptors, the R-M system, the DISARM system, the superinfection exclusions (SIEs) system, the abortive infection (Abi) system, and the adaptive immune system CRISPR-Cas all make phages resistant [132,133]. Hussain studied the evolutionary trajectory of resistance in wild-type phages, which showed that the rapid evolution of
mobile phage defense elements (PDEs) drove bacterial resistance to phages [134]. Studies have shown an evolutionary trade-off between phage and antibiotic resistance, with bacteria sometimes showing increased susceptibility to antibiotics when phage resistance evolves. Barber studies have demonstrated that efflux pumps play a dual role in antibiotic resistance and phage sensitivity, and when phage resistance leads to the loss of bacterial capsules, they will subsequently become sensitive to antibiotics [135]. However, when Burmeister studied E. coli phages, it was found that bacterial interaction with phages may depend on efflux pump protein TolC and structural barrier molecule lipopolysaccharide (LPS), and when these two mutants were constructed, some phage resistance mutations conferred an increase in antibiotic resistance [136]. Therefore, there are not only synergistic effects but also antagonistic effects between phages and antibiotics, and their intrinsic mechanisms of action remain to be further studied. In addition, phages replicate only in the target bacteria at the site of infection and treatment causes fewer adverse effects and is safer. Oral phage preparations are generally harmless and researchers have found the presence of adverse effects associated with phage therapy when assessing animal and clinical phage therapy safety and toxicity, but with a small probability of events [137]. Finally, phages are widespread in the environment and provide an inexhaustible resource. It only takes days to weeks to produce a new natural phage preparation, and if a phage develops resistance, phages that use other new receptors can also be quickly found. Screening for a new natural phage preparation takes a few days, and phages using other new receptors can also be quickly found if the phage develops resistance.

Despite the favorable results of various studies on phage applications, phage therapy still has certain shortcomings and unknowns. First, there are still some potential risks associated with the application of phage therapy, which are largely observational with existing phage therapies or performed in small non-randomized trials, where side effects may be underestimated. Second, the route of administration, frequency of administration, dose, phage resistance, pharmacokinetic and pharmacodynamic characteristics of phages, and the mechanism of phage entry into eukaryotic cells and the immune system need to continue to be studied in depth [40,138]. Third, legal regulation is a significant obstacle to the implementation of phage therapy and regulatory authorities classify phages as biological substances, which differs from the approval and production of antibiotics, making it difficult to use phage therapy. European legislators have been advocating for a regulatory framework specifically targeting individualized phage preparations but they have been strongly resisted [139]. Fourth, considering phages are natural entities, they entrap pharmaceutical companies in intellectual property issues [121]. Fifth, animal prophylactic phage products do not remove phages immediately after use and may lead to phage mutation and the cultivation of phage mutants. This problem also needs to be solved by using the regular rotation of phages and continuous detection, such as antibiotics [35]. Sixth, phages can transfer bacterial resistance genes and even contain toxic genes, implying that, as much as possible, the selection of lytic phages ensures that therapeutic phage products must be deeply purified and must remove endotoxins during processing [140]. Seventh, when the scope of phage application expands, including antibiotic substitutes, carrier delivery drugs, vaccines, and phage display technology, the demand for large-scale production of phage increases. The Phage on Tap (PoT) protocol has been studied for the rapid formulation of high titer phage formulations and a systematic procedure has also been developed for the isolation, up-culture, concentration, and purification of phages for pharmaceutical use [141]. The procedure can combine modified classical techniques, modern membrane filtration processes, and no organic solvents in 16 to 21 days, producing an average of 23 mL of $10^{11}$ PFU/mL phage [142]. Despite the enormous efforts of researchers for phage technology, there remain challenges for the production and expansion of wild-type phages for biological control. Finally, doctors and the public at large are unaware of the use of phages to treat diseases and the public believes that viruses are exclusively harmful to the human body, not realizing that they may also be beneficial [143].
8. Conclusions and Prospects

Antibiotic resistance poses a threat to global health. Russia approved the addition of phages to the official pharmacopoeia in 2016. The European Pharmacopoeia included “phage therapeutic active ingredients and pharmaceutical products for human and veterinary use” in 2021. To ensure its safety and effectiveness, pharmaceutical authorities such as the FDA and EMA require that any modern phage therapy product meet GMP standards, which poses challenges [144]. According to the statistics, Figure 3C reveals that 20 countries began to develop phages and had phage products approved for use. According to the analysis of 123 products in 20 nations, Figure 3A reveals that 53% of the products were used for human health, and Russia, Georgia, and the United States have rich experience in phage therapy for human diseases. Figure 3B reveals that the FDA has approved twenty phage products for animals and food, but only seven investigational new drugs (INDs) for humans. Except for Russia and Georgia, which have focused on phage therapy for human diseases and have sold many phage products, phage product research and development in other nations remains to be further developed. Overall, phage products in the United States are rapidly developing and the FDA has also approved several products. In the future, as a novel alternative therapy under the “one health” approach, phage research and development will continue to focus on making products that are environmentally friendly, safe, and successful in combating AMR.

Figure 3. Total phage products are distributed and approved. (A) The proportion of phage products in plants, animals, food, and humans. (B) The number of phage products that have been approved by the FDA and are in clinical research and marketed for human use. (C) Worldwide distribution of the number of phage products.
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