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Review

Phages in Fermented Foods: Interactions and Applications

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Abstract: Phage ecology has attracted increasing attention in recent years. Fermented foods have rich and diverse microbial communities, which are not only the creators of the unique flavors in food, but also good hosts for bacteriophages. However, at present, much is known about the bacterial and fungal communities and their functions in fermented foods, but little is known about the bacteriophages that inhabit the bacteria. This article reviews recent findings on phage diversity in fermented foods, highlighting how these organisms influence and relate to the dynamics of microbial communities in fermented foods. The application of bacteriophages in fermented food is also discussed, which will help to better control the food fermentation process in the future and promote its further development by the food industry.

Keywords: phage; fermentation; microbial community; interaction; application

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1. Introduction

Bacteriophage (bacteriophages, phage) were first discovered by Gill et al. in 1915 [1]. In 1917, Wilkinson et al. made a new breakthrough in the potential application of bacteriophages for the treatment of bacterial diseases, which was the result of their many years of experiments using bacteria as biological control agents for locusts [2]. Since then, the study of viruses and bacteriophages has explored their growth, existence, and interactions with host cells and has also led to the development of new relationships among biology, physics, chemistry, technology, and materials science, including groundbreaking research progress [3], such as in the discovery and application of nanomaterials [4]. Phages are also used in various biotechnological applications, including phage display, bacterial detection, biofilm degradation, and pathogen biocontrol [5]. In recent years, bacteriophages and other viruses have been used as biomaterials due to their advantages and potential in various fields, such as antibacterial therapy, cancer therapy, drug delivery, and novel vaccinations [6]. Numerous reports indicate that phages affect cells during their exponential growth phase and that they are able to eliminate targets as effectively as other highly specific antimicrobials. Due to their specificity, biosafety, and other advantages, bacteriophages can effectively fight multidrug-resistant bacterial infection and avoid non-targeted bacterial interference, and therefore they have more advantages than traditional antibacterial agents [7–9]. Phages, in similarity to most viruses, have no envelope [10], which is more conducive to their role in medical treatments. Bacteriophages are tiny and do not have a complete cell structure. The absolute logarithmic size is within 20 nm, the diameter or length can reach 1 μm, and the capsid, which contains the nucleic acid (DNA or RNA), is comprised of 100–1000 protein monomers [11,12]. Bacteriophages must be parasitic in living bacteria and have strict host specificities, which depend on the molecular structure and complementarity of phage adsorption organs and receptors on the surface of the recipient bacteria. Phage genomes contain many genes, most of which require bacterial ribosomes, various factors required for protein synthesis, and various amino acid and

energy production systems to achieve their own growth and proliferation. Once outside the host cell, the phage can neither grow nor replicate on its own [12].

Bacteriophages are the most abundant and diverse living organisms on Earth. Bacteriophages can usually be found in places full of bacterial communities, such as soil and animal guts. Based on statistical analysis, there are 10^{31} species of bacteriophage, which is ten times more than that of bacteria, and the place in the world with the highest abundance of bacteriophage is the sea [13]. Research has also shown that the viral community in fermented foods is less complex than that in other environments, such as seawater and soil. Approval by the relevant authorities to grant GRAS (generally recognized as safe) certification to bacteriophages has allowed their application in food, which has stimulated researchers to explore useful and valuable new phage resources.

Fermented foods occupy an important position in the global food industry and include various types of products, such as fermented dairy products, meat, grains, pulses, vegetables, seeds, roots, and alcoholic and nonalcoholic beverages. Fermented foods are popular for their special organoleptic qualities, flavor properties, and nutritional value. The principle of fermented food is to transform or generate alcohols, acids, esters, CO_2, and other substances through the action of microorganisms from the substances contained in the raw materials themselves.

Bacteria and yeast are present in all stages of fermentation and play a vital role in fermentation. There are many kinds of fermented foods and beverages, and the main types in Asia are sauerkraut, kimchi, stinky tofu, sausage, yogurt, cheese, bread, and rice wine [14,15]. Probiotics are naturally occurring microorganisms that are used in fermented foods and can also improve the body's health and microbial balance and help prevent and treat certain diseases [16]. The use of microorganisms to ferment food has a long history. Yogurt and cheese in North Africa can be regarded as the oldest fermented food, dating back to 7000 BC, and Egyptian bread and beer have a long history dating back to 3000 to 4000 [17,18]. Currently, most probiotics used to ferment dairy products on the market are all bacteria, including *Streptococcus*, *Leuconostoc*, and especially lactic acid bacteria (LAB), which are the main bacteria used in the production of various fermented dairy products [19,20]. In 1935, bacteriophages were first discovered to have the ability to cause the failure of industrially fermented dairy products, including yogurt, butter, cheese, and other dairy products. Although their economic impact on the dairy fermentation industry has not been specifically reported, research is warranted to avoid a more severe impact from their proliferation. Bacteriophages are considered natural antimicrobials in food because they can specifically infect and lyse food-borne pathogens without affecting other beneficial microbiota. Previous studies isolated two transfected lytic phages of *Staphylococcus aureus* in dairy products, indicating that phages have potential as pathogenic microorganism control agents, and the corresponding experiments using cheese finally confirmed this argument [20]. Yeast plays an important role in fermented products such as bread, alcoholic beverages, traditional fermented meat, and beans. *Saccharomyces cerevisiae* is one of the most commonly used yeasts, and wine, beer, Chinese liquor, rice wine, and other alcoholic beverages all rely on the role of *S. cerevisiae* [21]. Although yeast are fungi and do not have bacteriophages, studies have reported examples of phage lysis of pathogenic bacteria indirectly positively affecting yeast growth [21,22].

Overall, current studies show that fermented foods contain dense and complex phage communities. During the fermentation process of food, some microorganisms may be allowed to grow by inhibiting the proliferation of others. It is conceivable that bacteriophages can directly or indirectly benefit the product. Therefore, understanding the diversity of phages in food production and their interactions with microorganisms is of great significance. However, despite the growing number of descriptive articles on the presence and diversity of phages in fermented foods, there is still insufficient evidence that these organisms can influence food fermentation. This paper reviews the latest research results on the existence and diversity of bacteriophages in fermented foods, discusses the interaction between bacteriophages and microbial communities, lists applications in

fermented foods, and discusses the potential application value of bacteriophages to provide help to the fermented food industry in the future.

2. Phage Detection

2.1. Cultivation Methods

A good phage monitoring method facilitates the discovery of phages and enables biological control and food safety studies. The presence of viruses in fermented foods has traditionally been studied using culture-based methods for single bacteriophages and pathogenic viruses that cause fermentation defects [23]. In general, infectious phages are detected by their lytic properties on host bacteria. Therefore, the most important factor when developing assays for the target phage or phage group is the bacterial host strain. For the cultivation, isolation, and screening of phages in most studies, the double-layer agar method is used [24,25] to observe the formation of the disturbed areas (i.e., the formation of the plaques) [26] to qualitatively analyze the presence of phages (turbid plaques for lysogenic phages, clear plaques for lytic phages) [27]. Phages can be isolated by the spot method, stained, and examined by transmission electron microscopy (TEM) [28–30], and phages of different shapes and sizes can be displayed. For example, Hakdong Shin [31] et al. screened phages that could kill *Bacillus cereus* from 47 traditional fermented foods and isolated (purified) 14 phages. Among them, JBP901 was specific to the *Bacillus cereus* group, and transmission electron microscopy analysis showed that JBP901 is a member of the *Myoviridae* family. The results of bacterial analysis studies show that JBP901 can be used to control the growth of *Bacillus cereus* in liquid culture and food. Sunthornthummas [32] showed for the first time that a lactic acid bacteria (LAB) phage was isolated and identified from abnormally fermented milk from a Thai factory. The results of the study showed that only one LAB isolate was obtained. The LAB isolate was identified by API 50 CHL, 16S rDNA sequence analysis, and PCR with species-specific primers designed to differentiate the *L. casei* groups. Based on the above evidence, the isolate was identified as *Lacticaseibacillus paracasei.* Small plaques were formed on double-layer agar plates, and the *L. paracasei* phage was designated FT25. Transmission electron microscopy showed that phage FT25 had a hexagonal head (diameter 55 $\pm$ 4.6 nm) and a noncontracted tail (length 184 $\pm$ 7.8 nm) and belonged to Bradley's group B of the *Siphoviridae* family. In addition, Denis Rajnovic [33] used the fluorescence properties of resazurin to develop a rapid detection method to determine whether the target phage exists in the cultured sample. In general, the advantages of this method are the simplicity and low cost of culturing phages from agar plates and the ability to accurately obtain or identify target phages. For example, it is necessary to determine the culprit of yogurt fermentation failure. However, the operation process is cumbersome, the efficiency is not high, the results cannot be obtained quickly, the host needs to be susceptible to infection, and the diversity of bacteriophages in fermented food cannot be determined.

2.2. The Culture-Free Method

In the past, the virulence of phages or their corresponding host susceptibility, and serological studies were used to identify phages infecting LAB. In 1983, Jarvis was the first to use DNA–DNA hybridization technology, which allowed the analysis of phage affinities. Deveau et al. further revised this classification in 2006, using more rigorous DNA-DNA hybridization and sequence analysis [34]. In recent years, culture-free methods have mostly been used to qualitatively analyze phages. High-throughput sequencing, genome sequencing, and metagenomics are used for phage detection in food. In a review by T Paillet [35], several methods to directly count or observe the viruses present in a sample were summarized, such as flow cytometry, hyper-fluorescence microscopy, nanoparticle tracking analysis, interference light microscopy, scanning electron microscopy, transmission electron microscopy, and cryo-electron microscopy, but only a few studies have used these methods. The superiority of high-throughput sequencing for the detection of phages has mainly been demonstrated in recent articles. A study by Zünd M et al. [36]

demonstrated that prophages can be mapped using high-throughput sequencing, their activity can be quantified, and their replication can be studied to determine phage-to-host ratios that accurately map induced phages in the reference genome by ratio differences. Additionally, in a study by Sabrina Sprotte et al. [37], a Bulgarian strain in the study was isolated from a Nigerian fermented dairy product called nono. According to the genome sequencing results, the phage can be classified into the group B *Lactobacillus delbrueckii* phages, with a genome size of 31,399 bp and a GC content of 41.6 mol%. Hou et al. [38], using high-throughput sequencing and newly designed primer pairs on filtered sediment samples from different oceans and lakes, found that most of the sequences detected in the samples belonged to algae, and deep sequencing showed more completeness than shallow sequencing. It also confirmed that the greater the distance between the sampling points, the greater the difference in the algae community, and therefore high-throughput sequencing became a good method to understand the diversity of viral phages. Zheng [39] et al. used Illumina MiSeq high-throughput sequencing and 16S rDNA sequencing to isolate and identify lytic phages from the dominant mesophilic aerobic bacteria population during the natural fermentation of cucumber pickles. These authors used *P. fluorescens* J5415 and *E. cloacae* J01 as host bacteria to isolate lytic phages PspYZU5415 and EcpYZU01, respectively. The whole genomes of PspYZU5415 and EcpYZU01 were sequenced to determine their evolutionary relationship. Both phages exhibited broad host ranges and robust lytic activity, their genomes were free of toxin and antibiotic resistance genes, and their genome sequences indicated that they were novel and safe phages. In general, culture-free direct detection methods can quickly provide important data on the total number and diversity of phages present in a sample. However, since many phages share similar morphological characteristics, more precise techniques are also required to correctly characterize the specific composition of phage communities in fermented foods. The phage detection flow chart is shown in Figure 1.

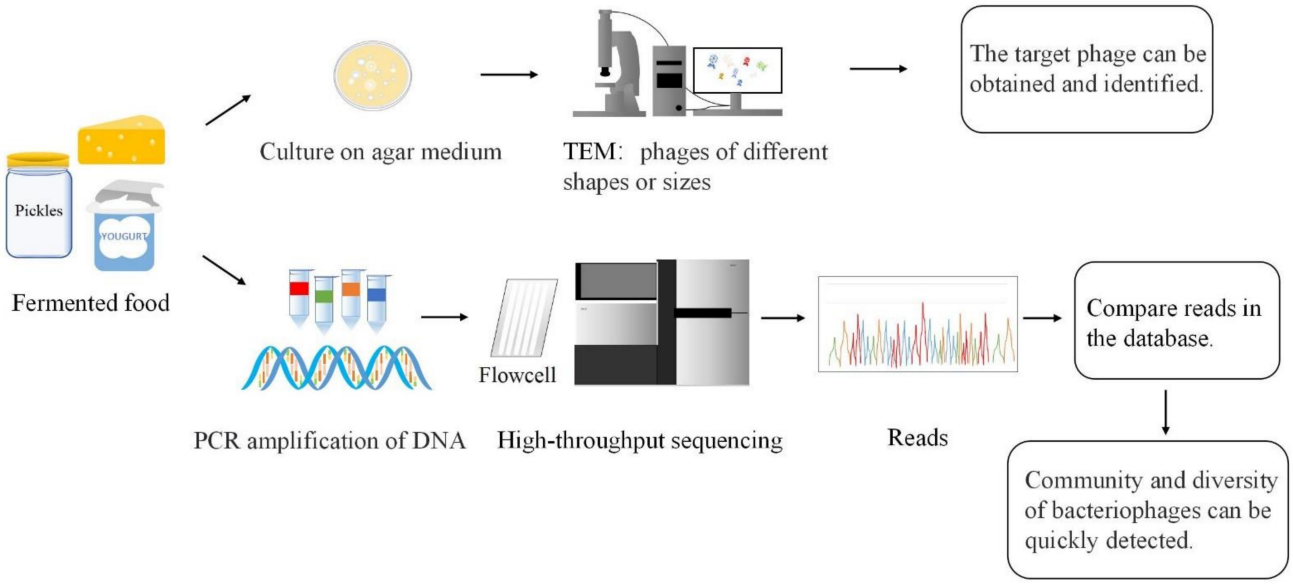

Figure 1. Phage detection flow chart. It shows that culture-based and culture-free methods to detect the presence and diversity of phages in fermented foods.

2.3. Diversity of Phages in Fermented Foods

Table 1 shows a summary of phages isolated from many fermented foods in the past decade. Among them, the long-tailed and muscle-tailed phages are dominated by *Siphoviridae*, *Myoviridae*, and *Podoviridae* are also occasionally isolated. The host is dominated by the dominant flora in the corresponding fermented food, such as lactic acid bacteria in kimchi and dairy products. There are a large number of studies reporting that bacteriophages infect lactic acid bacteria and affect food quality [40–43]. There are only a few research reports

on other important hosts, such as *Bacillus subtilis* in fermented bean products (natto) and especially *Enterobacter* and *Escherichia* in fermented cucumbers [44–46]. It is worth noting that there are very few studies describing that bacteria harmful to *Saccharomyces cerevisiae* were lysed by phages [21], such as grape strains that produced a new highly virulent phage (Kbarr-1) that was isolated and used for winemaking, which killed all strains known to be harmful to *Saccharomyces cerevisiae* and to other non-yeasts. The Kbarr-1 phenotype is encoded by the medium-sized 1.7 kb dsRNA TdV-Mbarr-1, which appears to be dependent on the large-sized 4.6 kb dsRNA virus (TdV-LAbarr) for stable replication [47].

Table 1. Phages isolated from fermented foods in the past ten years.

Types of Fermented Foods	The Strain (Host) Used for Phage Isolation	Phage Group	Nature	Form	References
Kimchi	Lactic acid bacteria	*Podoviridae*	lytic phages	Regular polyhedron head + soft tail	[40]
Fermented dairy products	Lactic acid bacteria	*Siphoviridae*	lytic phages	Hexagonal head + a long noncontracted tail	[42,43]
Fermented soy products	*Bacillus subtilis*	*Spounavirinae*	lytic phages	Regular icosahedron + tail	[26,44–46,48]
Cheese	*Ligilactobacillus salivarius*, *Lactobacillus*	*Myoviridae*	lytic phages	Not mentioned	[49,50]
Fermented olives	*Lactiplantibacillus plantarum*	Not mentioned	Not mentioned	Not mentioned	[51]
Fermented corn	*Lactobacillus*	Not mentioned	lysogenic and lytic phages	Not mentioned	[52]

3. Interactions between Bacteriophages and Fermenting Microorganisms

Phages are generally characterized by their life cycle. Lytic or lysogenic phages are ideal control tools because their proliferation can kill target bacteria. In contrast, lysogenic phages have no control effect because they can integrate their own DNA into the host genome and instead promote the spread of antimicrobial resistance or virulence through horizontal gene transfer [53]. Phages can be classified according to their infection strategy: (1) whether virion release occurs, which can be divided into two types: productive infection or a lysogenic, pseudolysogenic, or phage vector state; (2) the method of virion release (lysis and chronic release); (3) the genetically determined degree of the lysogenic cycle (lysogenic or lytic bacteriophages) [54]. A diagram of the phage adsorption-lysis step (using T2 phage as an example) is shown in Figure 2.

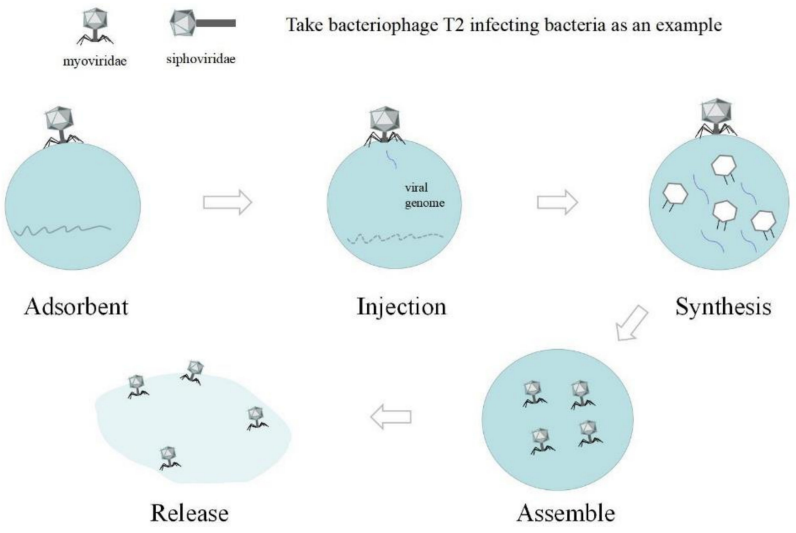

Figure 2. Phage infection process.

3.1. Genetic Basis of Lactic Acid Bacteria (LAB) Phages

Since its first discovery, LAB have been a stubborn, persistent, and costly problem in dairy fermentation [55]. While aseptic procedures, rotational incubation, sterilization, and improved starter culture systems have made great strides in controlling phage infections, they still pose serious risks, especially in today's large-scale production facilities, where fermentation is carried out on a very intensive and continuous basis. The development of genetic tools and sequencing technologies has greatly advanced our understanding of bacteriophage-host interactions [56]. The low cost, fast turnaround time, and relative technical convenience associated with these technologies have facilitated the sequencing of hundreds of bacterial and bacteriophage genomes. Most phages infected with LAB belong to the Siphoviridae family, which contains a large number of bacteriophages with long and uncontracted tails and long or isometric capsids. The rest belong to the Myoviridae family (long, contractible tail) and the Podoviridae family (short, non-contractable tail). Lactococcal phages are currently divided into ten taxonomic groups based on morphology and DNA homology, with the species P335, 936, and C2 (all siphoviral bacteriophages) being the most commonly encountered in the dairy industry [57,58]. These data allow us to observe that all the proteins which make up the core of the long-tailed phage tail organelle and host adsorption device have striking structural similarities. The distal tail region of bacteriophages is thought to interact with host polysaccharide receptors on the cell surface, while the diversity of tail morphology reflects the diversity and specificity of the types of interactions that can occur between these phages and their hosts. The study by Durmaz et al. [59] was the first to describe in detail a virulent recombinant *Lactococcus* bacteriophage that obtained chromosomal DNA from *Lactococcus lactis*, elucidate the f31.1 exchange region DNA sequence, and determine the origin of replication. At least two different chromosomal sites were found to produce recombinant bacteriophages.

Since phage evolution is thought to be the exchange of functional modules through the loss or acquisition of genetic material between bacteriophages and between bacteriophages and their hosts (and with bacteriophages) [60–62]. This universal genetic arrangement may be a facilitator of genetic brewing to help bacteriophages permanently adapt to changing environmental conditions or seek to infect new hosts. Thus, a major advantage of modular evolution may be that it provides virions with easy access to a large number of functional specificities through homologous recombination. Therefore, evolution should be thought of as acting on functional modules, rather than on viruses themselves, which can be of different sizes, such as a chologenetic gene block, a single gene, or a protein domain coding sequence [63]. The first stage of any successful phage infection is the adsorption of receptor-binding proteins (RBPs) to suitable bacterial host cells. Typically, this includes initial reversible interactions with host cell receptors, and the co-evolution of RBPs and their bacterial receptors forces endless cycles of adaptation to bacteriophage-host interactions, which in turn adds diversity to phage adsorption mechanisms. After successful adsorption and penetration of the bacteriophage, the phage establishes a lytic source or undergoes a lysis cycle. Phage replication, whether temperate or toxic, leads to the co-evolution of bacteria and phage populations. Co-evolution promotes diversity by sequentially supporting the innovation of the lineage, which in turn favors innovation in other lineages. However, new critical innovations may occur less frequently than minor adverse innovations that are not adaptable [64].

Inevitably, bacteriophages will evolve to overcome any conformational changes in host receptors. Analysis of bacteriophage mutants with expanded or altered host ranges showed that point mutations in structural tail genes were the only requirement to overcome host receptor changes and improve host adsorption or infection with new strains [59,65]. This information underscores the importance of sequencing strategies to understand the evolutionary and molecular processes that allow phages to overcome host obstacles. In addition, this knowledge provides a platform for the development of anti-phage starter cultures that target relevant phage populations in the dairy industry, rather than individual parasites [66].

The primary interaction between phages and their hosts is based on the recognition of a host-encoded receptor by a structure at the distal end of the phage tail known as the receptor binding protein (RBP). The molecular players involved in this initial physical connection between LAB phages and their hosts have been the subject of intense scrutiny, particularly over the past decade. While there are multiple levels at which phages may interact with their hosts involving various different hosts and phage structures, these may be simplified into groups based on their receptor material: protein, carbohydrate, or (lipo)teichoic acid [67]. *Lactococcus* 936 and P335 bacteriophages are thought to recognize glycan moieties located on the cell surface that are part of so-called cell membranes or cell wall polysaccharides (CWPS) [68]. In the latest research results on bacteriophage-bacterial interactions, the transcriptome and proteomic responses of the bacteriophage UCMA 16,447 Lactobacillus (LAB) Sucralosebacter UCMA 21,115 isolated from cider to phage UCMA 122 lytic infection, during phage infection, were differentially expressed at T by 215 and 16,447 genes, respectively, compared to uninfected conditions. Proteomics studies confirmed the same trend, with a total of 28 differentially expressed proteins found at T. Overall, genes encoding cellular functions, such as carbohydrate metabolism, translation, and signal transduction were downregulated, while genes involved in nucleotide metabolism and controlling DNA integrity were upregulated on phage infection. The work also highlights that phage infections inhibit many genes involved in bacterial cell movement and affect glycolysis [69].

3.2. Mechanism of Phage Binding to Receptors

Toxic *Lactococcus* phages of the *Siphoviridae* family are responsible for the failure of industrial milk fermentation worldwide, and a better understanding of the molecular mechanisms by which phages interact with their host bacteria is necessary to develop effective strategies to combat infection. In the first step of the phage infection process, the phage must recognize and attach to the host cell, which is the first point of host specificity. This attachment occurs through an interaction between the host receptor and the phage.

As early as 2004, Dupont et al. [70] identified the RBPs (receptor-binding protein) of 936 bacteriophages sk1 and bIL170 by constructing chimeric phages, and revealed the genetic elements encoding their presumed sugar receptors on the surface of host cells, which is undoubtedly one of the most important turning points in the interaction between *Lactococcus* bacteriophages and host. In *Lactococcus* bacteriophages, cell surface polysaccharide seems to be the main receptor material. The specific composition and arrangement of these sugars determine the specific interaction of bacteriophages [71].

In a study by Farenc [72], the authors revealed for the first time the molecular mechanism by which *Lactococcus* phage recognizes host receptors, showing a strong genomic similarity to *Listeria* phage. These authors reported the X-ray structure of phage 1358RBP in a complex with a monosaccharide. Each monomer of the trimeric RBP consists of two domains, and two sites were identified on the RBP surface, one accommodating the GlcNAc monosaccharide, and the other accommodating the GlcNAc or glucose 1-phosphate (Glc1P) monosaccharide. GlcNAc and GlcNAc1P are components of polysaccharide particles, and polysaccharides were identified on the cell surface of phage 1358's host, *Lactobacillus lactis* SMQ-388.

Phage-encoded host-specific proteins (TAL-RBPs) are major determinants of host recognition and attachment [73]. In a study by Lavelle et al. [42], detailed bioinformatics analysis revealed that regions involved in host recognition are often represented by predicted carbohydrate-binding domains. This finding solidifies the concept that *S. thermophilus* phage recognizes carbohydrate surface receptors. In addition, the presence of cell wall polysaccharide or teichoic acid-interacting domains in the second substrate protein (BPP) provides advantages for the complex interactions between the phage and the host. Structural bioinformatics is a very useful tool. A study by Chapot-Chartier [74] also showed that the bacterial cell wall plays a key role in these interactions. First, phages must attach to bacterial surfaces through specific interactions with receptors that are components of the

cell wall. In the next step, the phage must overcome a barrier composed of cell wall peptidoglycan (PG) to inject DNA into the bacterial cell. Additionally, at the end of the infection cycle, phages synthesize endolysins capable of hydrolyzing PGs and lysing bacterial cells to release phage progeny.

In recent years, *Streptococcus salivarius subsp. thermophilus* phages have been shown to recognize carbohydrate receptors on the host surface phages are either distributed regularly along the cell or located at the site of cell division. Their data suggest that phage adsorption to *S.thermophilus* is mediated by glycans associated with the bacterial cell surface [75]. Specifically, the PAC-type phage CHPC951 adsorbs to polysaccharides anchored to peptidoglycan, while the 987-type phage CHPC926 recognizes extracellular polysaccharides associated with the cell surface. Finally, it was found that the bacteriophage mutants of *Streptococcus thermophilus* had mutations in the genes encoding the carbohydrate biosynthesis pathway, including the gene of *RGP* (rhamnose-glucose polysaccharide) operon.

The experimental data of Marcelli B et al. confirmed that gene mutation was the cause of the resistance of four kinds of *S.thermophilus* (BIMs) to phage CHPC971 [76]. According to the data glucose, galactose, rhamnose, and glucosamine are the main sugar components of *L. lactis* [77]. To determine which sugar plays a key role in the interaction of phage CHPC971 with the host, they performed a competition assay. When phage infection was monitored in the LM17 medium, the final concentrations of glucose, galactose, and glucosamine at 250–243 mM did not retard the infection of strain CH_LC01 by phage CHPC971. On the other hand, rhamnose almost completely prevented phage infection at the same final concentrations, indicating the importance of this sugar in host recognition by phages.

In the latest study [78], Biochemical analysis of cell wall fractions of strains UCCSt50 and *Streptococcus thermophilus* B1 identified mutations within *orf*06955$_{\mathrm{UCCSt50}}$ resulting in loss of side-chain decoration of the *RGP* backbone structure. This study confirms that the *RGP* gene cluster of *Streptococcus thermophilus* encodes a mechanism for the biosynthesis of cell surface-associated polysaccharides that is critical for brucellosis binding and subsequent infection, thereby enhancing our understanding of the thermophilic streptococcal phage-host interaction.

3.3. Phage Resistance Mechanisms

In most environments, a large number of bacteriophages and hosts participate in the continuous co-evolution cycle, in which the host that is not sensitive to bacteriophages helps to preserve the bacterial lineage, while the drug-resistant bacteriophages threaten these bacterial strains. Therefore, phages and phage resistance mechanisms play a key role in the regulation of the bacterial population in most habitats.

3.3.1. Preventing Phage Adsorption

The adsorption of phages on host receptors is the first step of infection, and perhaps one of the most complex events because phages must recognize specific host-specific cell components. Phages are faced with the amazing diversity of host membranes and cell wall composition. In addition, bacteria have evolved a series of barriers to prevent bacteriophage adsorption. These adsorption-blocking mechanisms can be divided into at least three categories: the blocking of bacteriophage receptors, the production of extracellular matrix and competitive inhibitors, and the blocking of bacteriophage receptors [79–81].

3.3.2. Preventing Phage DNA Entry

The superinfection exclusion (Sie) system is the protein that blocks the entry of phage DNA into the host cell, thus conferring immunity to the specific phage. These proteins are predicted to be membrane-anchored or associated with membrane components [82–84]. Cor is an outer membrane (OM) lipoprotein, which plays a significant role in Sie systems [75]. Cor impedes superinfection by blocking the DNA entry by deactivating the phage receptor called ferrichrome uptake protein(FhuA) [75].

3.3.3. Cutting Phage Nucleic Acids

Restriction-modification systems. Many bacterial genera have the r-m system, whose main function is thought to be the protection of cells from DNA invasion, including viruses. Their activity is composed of several heterogeneous proteins [76]. These systems are composed of a restriction endonuclease (REase) and an associated methyltransferase (mTase) [85]. REase recognizes the unmethylated DNA in such motifs and degrades them. R/M systems are generally classified into four types according to their subunit composition, recognition site, and mechanism of action [86].

3.3.4. CRISPR-Based Prokaryotic Adaptive Immune System (CRISPR-Associated System, Cas)

In bacteria and archaea, clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated (Cas) proteins constitute an adaptive immune system against phages and other foreign genetic elements, responsible for protecting prokaryotic cells from invaders [87]. This system plays a defensive role as an adaptive immune mechanism. In exposure to an invader phage through an adaptive activity, the CRISPR/Cas system scans the genome of the phage and cleaves a fragment of this genome, flanked in the upstream of protospacer adjacent motif (PAM) [88]. Cleaved fragments (also known as spacers) are introduced into the CRISPR array and are placed between the direct repeats [89].

3.3.5. Abortive Infection Systems (Abi)

In the final stages of phage infection, bacteria can trigger a suicide response called abortive infection (Abi), which prevents infection from spreading to infected cells in other hosts to commit suicide before the phage completes its replication cycle, thus protecting bacterial colonies. Abi strategy manifests itself as a large number of mechanically diverse defense systems abundant in the bacterial genome [90].

3.4. Positive Effects of Phages on the Fermentation Microbial Community

Phages play a unique and active role in breaking down the corresponding host bacteria and releasing intracellular products. Although bacteriophages are considered detrimental to fermentation in the production of dairy products [91], some studies have found that phage lysis of cells helps the growth of dominant bacteria in the fermentation process, and the released substances can further promote the growth and function of beneficial bacteria. This was illustrated by Ma et al. [92], who studied the interaction between *Lacticaseibacillus casei* and *S. thermophilus* in the presence or absence of *S. thermophilus*-specific phages during milk fermentation. In addition, crude cell extracts isolated from thermophiles also significantly accelerated the growth and reproduction of *L. casei*, supporting the stimulating effect of phages on this microecosystem. It is worth noting that in the process of coculture fermentation, the fermentation time is reduced, and the number of *L. casei* cells is increased, with more *L. casei* in the dairy product leading to a sourer product.

Kimchi is a mildly lactic fermented vegetable and is a popular traditional dish in China, Japan, and Korea. The spoilage by spoilage bacteria and the accumulation of nitrite during vegetable fermentation are common problems affecting the health of the pickle industry and consumers. Komora et al. [93], using cucumber juice as an example, showed that the combined use of bacteriophages and lactic acid bacteria strains can control dominant mesophilic anaerobes (MABs) and reduce nitrate production in the early stage of pickle fermentation. *Pseudomonas fluorescens* and *Enterobacter cloacae* were the main MABs, and lytic phages PspYZU5415 and EcpYZU01 were isolated from them, respectively. A combination with phage MIX can effectively inhibit the growth of the host bacteria. Phage MIX combined with *Lactobacillus plantarum* M6 reduced the counts of *Pseudomonas* spp. and *Cloacillus* spp. to undetectable levels during the fermentation of artificially contaminated cucumber juice. Furthermore, the nitrite content increased to 11.3 mg/L at 20 h and was then completely degraded at 36 h. In the group without phage MIX, the presence of *Pseudomonas* spp. and *Cloacillus* spp. was detected during the fermentation process (0–48 h),

and the nitrite content in the control group rapidly increased to 65.7 mg/kg at 12 h. L and decreased to 21.6 mg/L at 48 h. These studies suggest that phages have a positive regulatory effect on microbial communities.

3.5. Negative Effects of Bacteriophages on Fermenting Microorganisms

After bacteriophage infection, bacterial growth is inhibited, and beneficial substances are degraded. In a study by Ghosh et al. [26], phage BSP10 infecting *B. subtilis* was isolated and further characterized. In addition, bacteriophage BSP10 effectively inhibited the growth of *B. subtilis* in a fermented soybean food. During fermentation, the number of bacteria was reduced 112-fold compared to the control (no phage). In addition, the authors experimentally demonstrated for the first time that the *B. subtilis*-infecting phage greatly enhanced the degradation of polyglutamic acid during soybean fermentation, which may negatively affect the function of the food [48].

Whether it has a positive or negative effect, the general idea is that the phage infects the host bacteria, inhibiting its growth rate or lysing it and releasing effective factors. Therefore, we can use phages that are good for fermentation in production.

4. Application of Bacteriophages in Fermented Food

4.1. Bacteriophages as an Ideal Antibacterial Agent

While bacteriophages are extremely harmful to the dairy industry, nonthermal food processing and the replacement of chemical additives with natural antimicrobials are promising trends in the food industry that could reduce or even eliminate foodborne pathogens in a variety of foods, which is critical for semi-finished products. Processed and ready-to-eat foods are particularly beneficial. Table 2 shows the comparison of the advantages and disadvantages of common sterilization methods for fermented foods and bacteriophage antibacterial agents. Common sterilization methods include pasteurization, irradiation, high-temperature sterilization, and ultrahigh-pressure sterilization technology, which can be divided into thermal sterilization and nonthermal sterilization. Heat killing may cause the loss of flavor, taste, and nutrients. Although non-heat killing can allow the retention of the original flavor and nutrition to a great extent, it consumes a large amount of energy and may bring new risks. Therefore, it is of great significance to use bacteriophage as an antibacterial agent to kill certain harmful bacteria.

Table 2. Comparison of common sterilization methods with bacteriophage antibacterial methods.

Sterilization Method	Method	Types of Fermented Foods	Advantages and Disadvantages	References
Common sterilization methods	Ultrahigh-pressure sterilization technology	Pickles, yogurt	Advantages: no temperature change, can better retain the original color, taste, and nutrients Disadvantage: high energy consumption	[94–98]
	Irradiation Sterilization	Kimchi	Pros: thiamine can be stored for years after irradiation without refrigeration Disadvantages: high energy consumption, vitamins E and C will reduce or even eliminate mutations that may be caused through radiation and lead to radiation resistance	
	Pasteurization	Fermented peppers, yogurt	Advantages: better preservation of the nutrition and natural flavor of yogurt Cons: can store at 4 °C for approximately a week	

Table 2. *Cont.*

Sterilization Method	Method	Types of Fermented Foods	Advantages and Disadvantages	References
	High-temperature sterilization	Fermented fish	Advantages: high-temperature instantaneous sterilization can kill all live bacteria in a short time Disadvantages: changes in flavor and taste, some stubborn bacteria are sublethal	
Bacteriophage antibacterial method	Direct interaction with the host or indirect interaction with released particles	Cheese, fermented soy products	Advantages: no energy consumption, no additives, can improve flavor and quality. Disadvantages: can only inhibit or eliminate specific harmful bacteria	

Several reviews describe the potential role of bacteriophages in food safety [99–101]. In 2006, the U.S. Food and Drug Administration approved a product based on a phage against *Listeria* for use in cheese production. In Komora's study, the addition of bacteriophages as a non-heat-treated food processing process combined with pressure was used to eliminate *L. monocytogenes* in milk [93].

Although alternative preservation techniques, such as high hydrostatic pressure treatment, were used earlier to eliminate bacteriophages to improve food quality and safety, Zhang et al. [102] reported that the use of HHP treatment completely inactivated *Streptococcus thermophilus* phage. However, the elimination of *Listeria monocytogenes* using bacteriophage is of particular significance for the food industry and food safety. Many scholars have performed much research on this [103]. In particular, Komora et al. have successively verified the conditional method for the eradication of *Listeria monocytogenes* by Listex™) P100 combined with the bacteriocin peptide PA-1 under high hydrostatic pressure (HHP) treatment [104]. The final results showed that treatment at 400 MPa reduced phage titers below the level detected in all substrates, while at lower pressures, phage survival was substrate-dependent, and the acidic pH of the substrate might exacerbate the elimination effect. The initial phage content did not affect the inactivation rate during HHP treatment (300 MPa, 5 min, 10 °C) in cheese, sausage, or milk matrices and milk stored at 4 °C for 28 days, and "Monte de Estrela" phage titers were stable in these matrices after 60 days. The conclusion is that this is the only method that eliminates *Listeria monocytogenes* immediately after processing [105].

The latest research shows that the growth of *E. coli* is reduced when it is fermented after phage treatment during cheese making and maturation. In addition, image analysis of cheese slices revealed a significant reduction in the number of cheese eyes and the area occupied by pores throughout the cheese maturation process. Therefore, the use of bacteriophages as biological control agents provides an effective approach to combat early stomatal conditions in cheese [106].

Bacillus cereus is a food-borne bacterial pathogen that can cause diarrhea and vomiting. In one study, Bandara [107] investigated the usefulness of phages in eradicating *Bacillus cereus* from fermented foods. Thirteen phages were isolated from Korean fermented foods, and 2 (BCP1-1 and BCP8-2) were further characterized. Purified phage was used to inhibit the growth of *B. cereus* in a rapidly fermenting soybean product. BCP1-1 and BCP8-2 were effective in eradicating *B. cereus* from food only when divalent cations (Ca, Mg, or Mn) were added to the medium. Further studies show that divalent cations are essential for phage adsorption [108], while monovalent cations (Na) are essential for the post-adsorption phase of phage infection. Optimization of phage reaction conditions is critical for the successful utilization of phage biocontrol.

4.2. Bacterial Mutants Obtained after Bacteriophage Treatment as Starters for Fermented Food

Harmful bacteriophages in fermented foods affect the quality of products. Studies have shown that using bacteriophages to obtain mutant bacterial strains carrying resistance genes is an effective way to deal with harmful bacteriophages. On the one hand, harmful phage infection is avoided, and on the other hand, the food has better fermentation characteristics. The dairy industry uses mesophilic, gram-positive LAB to produce a range of fermented milk products. Milk fermentation processes are susceptible to contamination by toxic bacteriophages, but numerous phage control strategies are available [109]. The most effective of these is the use of LAB strains that carry a phage-resistant system, such as the abortive infection (Abi) mechanism [110]. However, the mode of action of most Abi systems remains poorly documented. de Lima further elucidated the antiviral activity of the *Lactococcus lactis* AbiT system [111].

Phage-insensitive *S. thermophilus* mutants were obtained by treating phage-sensitive industrial strains with lytic phages [112]. During fermentation, they form fermented milk curds that have a uniform, dense consistency with a pleasant taste and flavor. BIMs can be used as a starter to stabilize the fermentation process under phage infection conditions.

Briggiler Marcó previously characterized the probiotic potential of four spontaneous phage-resistant mutants isolated from *Lactiplantibacillus plantarum* ATCC8014 using phage. These natural mutants, with similar or improved potential probiotic properties in their susceptible strains, can be used in fermented food production processes to minimize failures due to phages [113].

However, there are other bacteriophages that are thought to be the causative agent of difficult malolactic fermentation (although this has not been proven) and are beginning to be considered as an alternative to the use of sulfur dioxide to prevent wine spoilage [47].

5. Conclusions and Outlook

The isolation of a large number of phages and viral metagenomics data have revealed the diversity of phages in fermented foods, mainly in families such as *Siphoviridae*, *Podoviridae*, and *Myoviridae*, most of which were present in bacteria such as *Lactobacillus* and *B. subtilis*. However, the impact of this diversity on the composition and function of microbial communities remains understudied and exploited.

From the current research, it can be concluded that the impact of bacteriophages on fermented foods can be divided into two aspects. One aspect is that phages are beneficial. We can use their positive effects on the microbial community of fermented foods to develop effective phages with broad-spectrum antibacterial activities. They can be used individually or in combination to make an ideal antibacterial agent that can infect multiple hosts to achieve food preservation. The second aspect is that bacteriophages are harmful. For such bacteriophages, we can use bacteriophages to obtain mutant fermentation strains carrying resistance genes and use their excellent characteristics to use them for food fermentation. In conclusion, we can make full use of the interaction between bacteriophages and fermented strains, alleviate the negative impact of bacteriophages on the fermented food industry, and promote the wide application of bacteriophages in food fermentation.

At present, few studies have proven whether there is a correlation between phage and bacterial population levels in the fermentation cycle. The related research is not thorough enough to analyze the relationship between the two. In the future, phages can be used to further explore the process of food fermentation, flavor production, and quality formation and to analyze the optimal conditions for the optimal effect of phage (such as pH and cation assistance) for the effective control of phage contamination in fermentation systems to reduce the risk of fermentation failure and to expand the application of phages in pathogen biological control. However, new developments may require more fine-tuning of microbial community composition and the development of improved anti-phage priming culture systems to achieve the conditions required for fermentation control.

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Abbreviations

GRAS	generally recognized as safe
TEM	Transmission Electron Microscope
PG	cell wall peptidoglycan
MAB	mesophilic anaerobe
HHP	high hydrostatic pressure

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