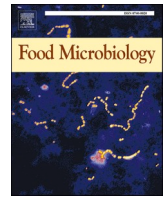




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Viruses in fermented foods: are they good or bad? Two sides of the same coin

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ABSTRACT

The emergence of Coronavirus disease 2019 as a global pandemic has increased popular concerns about diseases caused by viruses. Fermented foods containing high loads of viable fungi and bacteria are potential sources for virus contamination. The most common include viruses that infect bacteria (bacteriophage) and yeasts reported in fermented milks, sausages, vegetables, wine, sourdough, and cocoa beans. Recent molecular studies have also associated fermented foods as vehicles for pathogenic human viruses. Human noroviruses, rotavirus, and hepatitis virus have been identified in different fermented foods through multiple routes. No severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) virus or close members were found in fermented foods to date. However, the occurrence/persistence of other pathogenic viruses reveals a potential vulnerability of fermented foods to SARS-CoV-2 contamination. On the other side of the coin, some bacteriophages are being suggested for improving the fermentation process and food safety, as well as owing potential probiotic properties in modern fermented foods. This review will address the diversity and characteristics of viruses associated with fermented foods and what has been changed after a short introduction to the most common next-generation sequencing platforms. Also, the risk of SARS-CoV-2 transmission via fermented foods and preventive measures will be discussed.

1. Introduction

Viruses are ubiquitous in every ecosystem and infect all forms of life, from prokaryotes to eukaryotes (Hyman and Abedon, 2012). Food fermentation is driven by dense microbial consortia consisting mainly of bacteria and fungi (Pereira et al., 2020). This constitutes a rich reservoir for the development of many microorganism-infecting viruses. Studies

have reported the presence of viruses that infect bacteria (bacteriophages) and yeast in plenty of fermented food products, including wine, meat, cheese, yoghurt, sourdough, sauerkraut, kimchi, soybean, and cocoa (Aquad et al., 1997; Barrangou et al., 2002; Foschino et al., 2005; Illegheems et al., 2012; Kiliç et al., 1996; Kleppen et al., 2012a; Pringsulaka et al., 2011; Umene et al., 2009). In general, bacteriophages are considered harmful by decreasing the fermentative capacity of lactic

Abbreviations: BA, Biological amines; BLAST, Basic Local Alignment Search Tool; COVID-19, Coronavirus disease 2019; FAO, Food and Agriculture Organization of the United Nations; GIT, Gastrointestinal tract; HAV, Hepatitis A virus; HV, Hepatitis virus; HEV, Hepatitis E virus; HGT, Horizontal gene transfer; HTS, High-throughput screening; kb, Kilobases; LA, Linker amplification; LAB, Lactic acid bacteria; LASL, Linker amplification shotgun libraries; MERS-CoV, Middle East respiratory syndrome coronavirus; MG-RAST, MetaGenomic-Rapid Annotation using Subsystem Technology; NGS, Next-generation sequencing; NiV, Nipah virus; nm, Nanometer; NoV, Norovirus; MDA, Multiple displacement amplification; MLST, Multilocus sequence typing; ORF, Open reading frame; OUT, Operational taxonomic units; PCR, Polymerase chain reaction; PHACCS, PHAge Communities from Contig Spectrum; qPCR, Real-time quantitative PCR; RAPD, Random Amplified Polymorphic DNA; RFLP, Restriction Fragment Length Polymorphism; RT-PCR, Reverse transcription polymerase chain reaction; RV, Rotavirus; RVA, Rotavirus A; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TBEV, Tick-borne encephalitis virus; TEM, Transmission electron microscopy; UV, Ultraviolet; VACV, Vaccinia virus; VIROME, Viral Informatics Resource for Metagenome Exploration; VMGAP, Viral MetaGenome Annotation Pipeline; VP, Viral particles; WGA, Whole genome amplification; WHO, World Health Organization.

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acid bacteria (LAB) and yeasts, occasionally resulting in complete fermentation failure. The diversity of phages in fermented foods has been seen to vary according to geography, climate, environment, type of raw material, preparation methods, and microbial composition (Tamang et al., 2020). However, although there is evidence that bacteriophages can cause disease in humans (Tetz and Tetz, 2018), they are not associated with sanitary and public health concerns.

In addition to bacteriophages and yeast-associated viruses, pathogenic viruses have been reported in fermented foods causing injuries and even death (Cho et al., 2016; Colson et al., 2010; Holzmann et al., 2009; Hossain et al., 2016). The zoonotic Nipah virus (NiV), for example, was attributed as the probable cause of the death of eight victims who ingested a traditional fermented liquor in Bangladesh (Hossain et al., 2016). Viruses have high environmental resistance being able to survive against microorganisms elimination processes (Vasickova et al., 2010), using these products as vehicles to human contagion. Currently, human noroviruses (NoVs) are recognized as the main cause of viral foodborne outbreaks, followed by rotavirus (RV) and hepatitis virus (HV) (Leblanc et al., 2019). Contamination can occur in different ways, mainly through infected raw materials and improper food handling. RVs causes an estimated 111 thousand cases of diarrhea per year, two million hospitalizations, and 400 thousand fatalities in children under five years old, being more than 80% from undeveloped countries (Tamang et al., 2020; World Health Organization, 2009). The emergence of Coronavirus disease 2019 (COVID-19) as a global pandemic has increased popular concerns about diseases caused by viruses (Lai et al., 2020). Despite the principal form of spreading is human-to-human contact, the COVID-19 similar Middle East Respiratory Syndrome (MERS-CoV) virus remained infectious up to 60 min outside the body (Pyankov et al., 2018). Security authorities raised concern on viral transmission by food, as preparation and delivery can be critical step on transmission (Rizou et al., 2020).

The presence of viruses in fermented foods has traditionally been studied by culture-dependent methods. These methods are focused on singular bacteriophages that cause fermentative flaws and on pathogenic human viruses (Park et al., 2011). However, with the advancement of molecular techniques and the outgrowth of next-generation sequencing (NGS), a large body of metagenomic sequencing information was allowed, circumventing the need for gene cloning or cultivation (de Melo Pereira et al., 2020). Fermented food microbiome has been accessed, and what is known as “viromes” has emerged. However, the number of viromes studies still lags far behind that of bacteria and fungi publications; for each virome in 2019, there were 42 microbiome studies (Ledormand et al., 2020; Tamang et al., 2020).

The lack of a universal molecular marker, as the 16S and 18S rRNA in bacteria and fungi, respectively, can be considered an obstacle for virome studies in food matrices. Nevertheless, shotgun metagenomic, which does not depend on a target ribosomal marker, has successively characterized viral communities from freshwater, soil, ocean, mammalian gut and, to a lesser extent, fermented food products (Dugat-Bony et al., 2020; Hayes et al., 2017; Park et al., 2011). Recently, pyrosequencing and Illumina Miseq platforms have been used to characterize viral communities of different fermented foods (Dugat-Bony et al., 2020; Jung et al., 2018). NGS viromes confirmed the dominance of *Caudovirales* bacteriophages as on culture-dependent approaches (Dugat-Bony et al., 2020; Jung et al., 2018; Park et al., 2011).

NGS studies have enabled new applications and perspectives for bacteriophages and, thus, accessing the other side of the coin. It has been observed that some bacteriophages can modulate bacterial community succession during the fermentation process, positively affecting food quality and sensorial properties (Agyirifo et al., 2019). Quorum sensing studies have not yet been accomplished to better understand this modulation and relationship. Gastrointestinal tract (GIT) bacterial community is also shaped by bacteriophages contained in fermented foods, impacting host physiology and metabolism. They are able to trigger immune responses through direct contact with mucosal epithelial cells

(locally) or with immune system components (systemically) (Sausset et al., 2020). These features enable bacteriophages to provide probiotic effects, as suggested by Pacini and Ruggiero (2019), through the ingestion of phage-containing fermented milk and colostrum.

This review will provide a general overview of viruses associated with fermented foods and what has been changed after a short introduction to the most common NGS platforms, as well as a critical discussion on the potential of fermented foods to deliver viruses with public health concerns. Additionally, NGS strategies and methods for describing food viromes will be addressed with the ultimate objective of assisting future evaluation studies.

2. Bacteriophages and yeast viruses

Bacteria comprise a highly diverse group, representing the second major biomass element on Earth (~15%), behind only plants (~80%). This abundant living mass is a huge reservoir for bacteriophage (or simply called phage) predation. As phages can be found repeatedly in different hosts, they represent on approximately 10^{31} particles, ten times the number of bacteria (10^{30} cells) (Breitbart and Rohwer, 2005). Bacteriophages are small in size (isometric heads are typically 45–170 nm in diameter) and are composed of a single type of nucleic acid with single or double-stranded (ssDNA, dsDNA, ssRNA, dsRNA) protected by a protein or lipoprotein capsid (Orlova, 2012). Phage genomes vary between families ranging from ~3.5 kb (e.g. *Escherichia coli* phage genome) to ~540 kb (*Prevotella* spp. phages genome) (Sausset et al., 2020). They do not have cellular machinery required for transcription, translation, and energy production, using from their hosts. When inside, phage particles are formed and, when bacterial lysis occurs, they are released (lytic cycle). The phages that use only the lytic cycle to propagate are called virulent.

The infection of LAB by bacteriophages is widely investigated being considered the primary cause of fermentation failure in the dairy industry (Garneau and Moineau, 2011). However, some phages have specific genes to direct their integration into the bacterial chromosome and remain dormant as a prophage until stresses or specific conditions induce the lytic cycle. A bacterial host carrying a prophage is called lysogenic. A temperate phage can form lysogens and initiate either a lytic cycle or a lysogenic cycle, whereas a virulent phage is obligately lytic (Samson and Moineau, 2013).

Phages have various contamination routes during the manufacture of fermented foods (Fig. 1). Eventually, LAB can naturally prevent phage invasion by evolving phage-resistance systems, or it can be genetically engineered to avoid culture devastation (e.g., origin-derived phage-encoded resistance, gene silencing, suicide system, and subunit poisoning) (Murphy et al., 2017). The use of physical-chemical methods on materials and industrial facilities also acts in phage contamination prevention. Examples include thermal treatment, use of biocidal agents (sodium hypochlorite and peracetic acid), UV photocatalysis, and high-pressure treatments (high hydrostatic pressure and high-pressure homogenization) (Murphy et al., 2017). However, the existence of resistant viruses allows contamination to still occur (Fig. 1). Phage-related issues are not restricted to foods, but also pharmaceutical, chemical, and pesticide industries (Pujato et al., 2019).

A survey on bacteriophages and yeast virus's diversity in fermented foods is reported in Table 1. They are mainly represented by LAB phages (*Lactococcus*, *Lactobacillus*, *Leuconostoc*, *Enterococcus*, *Streptococcus*, and *Weissella*), being *Lactococcus*, *Lactobacillus*, and *Leuconostoc* most commonly reported in fermented foods (Pereira et al., 2020). Bacteriophages infecting LAB are all members of the *Caudovirales*, an order known as the non-enveloped dsDNA tailed phages. *Caudovirales* use the tail section to bind to the receptor on the bacterial cell wall, and the genome passes down the tail into the bacteria cell. Once inside, the virus genome is replicated by overlapping bacterial DNA and replicating the complete viral genome. Three families within the *Caudovirales* order, i.e., *Myoviridae*, *Siphoviridae*, and *Podoviridae*, were reported in fermented

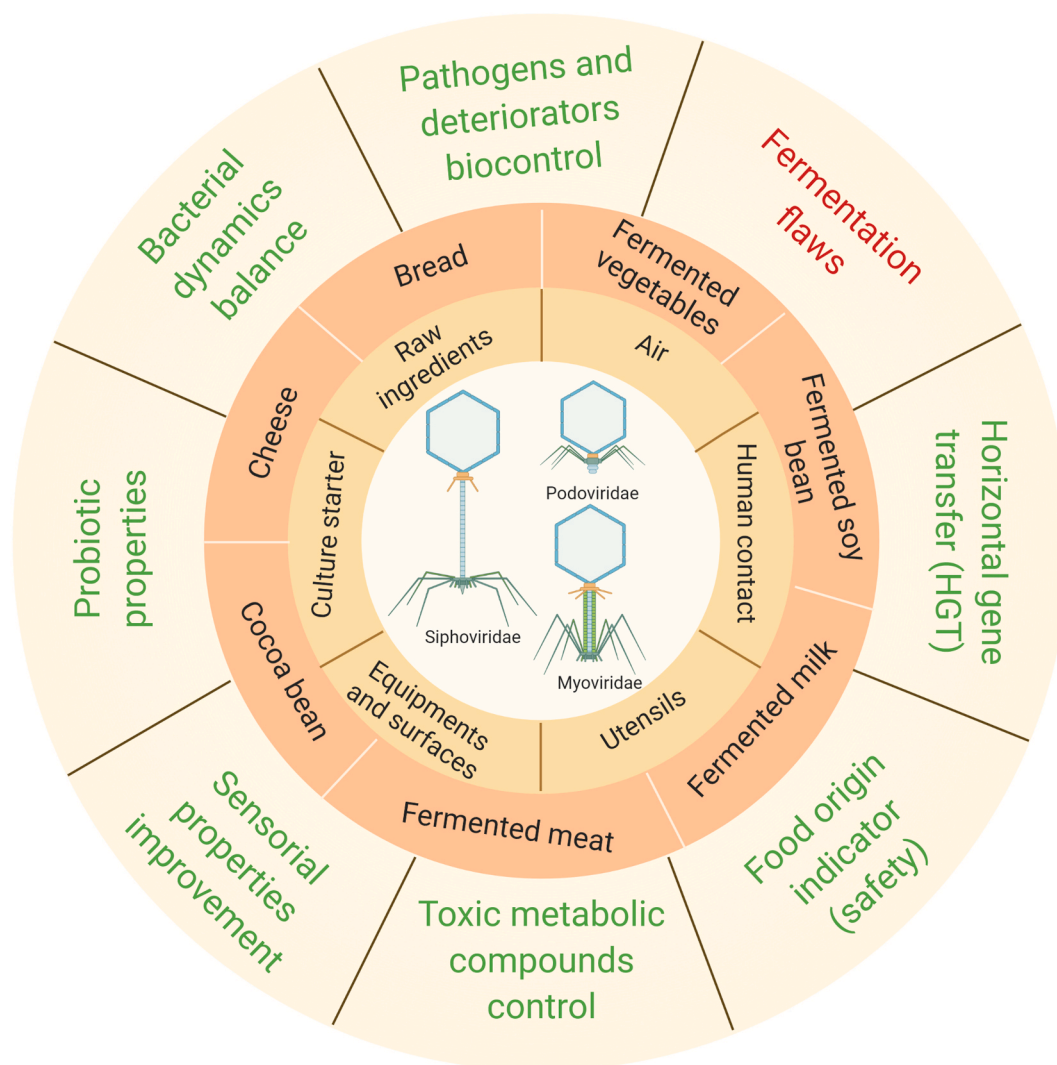


Fig. 1. Main bacteriophages families and contagion routes associated with fermented foods (adapted from Samson and Moineau, 2013). Positive associations are written in green and negative in red on the outer part of the circle. This figure was created using BioRender (<https://biorender.com/>). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

foods (Fig. 1). *Myoviridae* are characterized by the presence of a long contractile tail, *Siphoviridae* has a long, non-contractile tail, and *Podoviridae* a short, non-contractile tail (Samson and Moineau, 2013). This classification, which is based on morphology instead of DNA sequences, was originated by Bradley in 1969 and has been extended to date.

The first LAB phage report was published 85 years ago, a streptococci attack-phage in cheese (Whitehead and Hunter, 1947). Posteriorly, the presence of phage was widely reported during lactic fermentation (e.g., sauerkraut, yogurt, natto, and cucumber) (Barrangou et al., 2002; Brussow et al., 1994; Kiliç et al., 1996; Kleppen et al., 2012b; Lu et al., 2003b; McIntyre et al., 1991; Quiberoni et al., 2003; Saxelin et al., 1986; Umene and Shiraishi, 2013). Phage attack was frequently associated with fermentation failure until complete loss of the product batch due to unfeasibility of starter cultures (Quiberoni et al., 2003). Starter-destroying phages are not restricted to LAB. Other genera that compose starter cultures are also attacked by phages, such as *Bacillus* spp. in fermented soybean known as natto (Umene et al., 2009), *Staphylococcus* spp. in salami (Bruttin et al., 1992), and even on yeast (*Saccharomyces cerevisiae*) as called 'yeast viruses' in winemaking (Ramírez et al., 2015; Rodríguez-Couñiño et al., 2011). Differently from bacteriophages, *S. cerevisiae* viruses belong to the *Totiviridae* family (*Ghabrivirales* order) and infect not only yeasts but also protozoa, filamentous fungi, plants, invertebrates, and vertebrates (Rowley, 2017).

The presence of bacteriophages in microbial cultures is not itself sufficient for affecting fermentation processes. It depends on the microbial composition in the starter, being the more diverse the composition, the less chance of failure (Spus et al., 2015). This can be explained by the fact that bacteria have different levels of sensitivity to phages and, when an attack occurs, some bacteria are resistant and recover fermentation. Beyond that, contamination seems to be attributed to the consistency of the food matrix in which liquid matrices are more susceptible to allowing a rapid phage spread than solid or semi-solid. Bruttin et al. (1992) attributed the solid-state of meat in salami as the key factor to prevent attack by *Staphylococcus carnosus* bacteriophages, while liquid milk fermentation allows easiest phages propagation (Garneau and Moineau, 2011).

3. Human foodborne and zoonotic viruses

Food fermenters produce different end-metabolites having antiviral activity, including bacteriocins, hydrogen peroxide, ethanol, and lactic acid. However, some enteric viruses, including NoV, hepatitis A virus (HAV), hepatitis E virus (HEV), and *Orthopoxvirus* and *Henipavirus* genus, are allowed to remain viable in foods for periods from two days to four weeks (Hewitt and Greening, 2004), even in an environment with the lack of specific host cells to replicate. Contamination routes include

Table 1
Bacteriophages and yeast virus diversity in fermented food.

Phage	Fermented food	Reference
<i>Lactobacillus</i>	Yoghurt	Kiliç et al. (1996); Auad et al., (1997)
	Cocoa bean	Illegheims et al. (2012); Agyirifo et al. (2019)
	Meat	Trevors et al. (1983)
	Sourdough	Foschino et al. (2005)
	Sauerkraut	Barrangou et al. (2002)
	Kimchi	Jung et al. (2018)
	Fermented cucumber	(Lu et al., 2003a); (Lu et al., 2012)
<i>Lactococcus</i>	Cheese	(McIntyre et al., 1991); (Murphy et al., 2013); (Frantzen and Holo, 2019); (Mahony et al., 2017); (Dugat-Bony et al., 2020)
	Fermented milk and colostrum	(Pacini and Ruggiero, 2019)
	Fermented fish	Phumkhachorn (2012)
	Kem buk nud	Phumkhachorn (2012)
	Kimchi	Jung et al. (2018)
	Cocoa bean	Agyirifo et al. (2019)
	Cheese	(Kleppen et al., 2012b); (Kot et al., 2014); (Dugat-Bony et al., 2020); (Atamer et al., 2011)
<i>Leuconostoc</i>	Fermented milk villi	Saxelin et al. (1986)
	Sauerkraut	(Barrangou et al., 2002); (Lu et al., 2010); (Mudgal et al., 2006)
	Kimchi	(Jung et al., 2018); (Jung et al., 2011)
	Fermented pork meat	Greer et al. (2007)
	Cocoa bean	Agyirifo et al. (2019)
	Hard cheese and acid curd cheese	Ali et al. (2013)
	Whey and brine	Atamer et al. (2011)
	Butter milk and butter cream	(Ali et al., 2013); (Atamer et al., 2011)
	Cheese	(Ladero et al., 2016); (Del Rio et al., 2019)
	Cocoa bean	Agyirifo et al. (2019)
<i>Streptococcus</i>	Yoghurt	(Bendadis et al., 1990); (Brussow et al., 1994); (Quiberoni et al., 2003); (Ishlimova et al., 2012); (Ma et al., 2014)
	Cheese	(Whitehead and Hunter, 1947); (Brussow et al., 1994); (Quiberoni et al., 2006); (Zinno et al., 2010)
	Fermented milk villi	Saxelin et al. (1986)
<i>Weissella</i>	Fermented milk and colostrum	(Pacini and Ruggiero, 2019)
	Kimchi	(Jung et al., 2018); (Kleppen et al., 2012b)
	Fermented pork sausage	Pringsulaka et al. (2011)
<i>Oenococcus</i>	Fermented cucumber	Lu et al. (2012)
	Wine	Doria et al. (2013)
<i>Bacillus</i>	Natto	(Umene et al., 2009); (Nagai and Yamasaki, 2009); (Umene and Shiraishi (2013)
	Doenjang, Jangajji, Meju and Gochujang	Shin et al. (2011)
	Kinema	Kumar et al. (2019)
	Cocoa bean	Agyirifo et al. (2019)
	Kimchi	Jung et al. (2018)
	Cocoa bean	Agyirifo et al. (2019)
	Salami	Bruttin et al. (1992)
	Cocoa bean	(Illegheims et al., 2012); (Agyirifo et al., 2019)
	Cheese	Dugat-Bony et al. (2020)
	Cheese	Dugat-Bony et al. (2020)
Cheese	Dugat-Bony et al. (2020)	
<i>Propionibacterium</i>	Cheese	Cheng et al. (2018)
<i>Klebsiella</i>	Cocoa bean	Illegheims et al. (2012)
<i>Pseudomonas</i>	Cocoa bean	Agyirifo et al. (2019)
<i>Gluconobacter</i>	Wine	Philippe et al. (2018)
Yeast virus		
<i>Saccharomyces cerevisiae</i>	Wine	(Rodríguez-Cousiño et al., 2011); (Rodríguez-Cousiño et al., 2011)

(i) the raw material contaminated before food preparation, (ii) food preparation and processing, emphasizing the role of food handler, hygienic conditions, and the use of polluted materials, and (iii) food delivery and facilities routes where the food passes after it is finished (Fig. 3).

Tick-borne encephalitis virus (TBEV) outbreaks were associated with cheese made with infected goat's milk in Europe (Brockmann et al., 2018; Holzmann et al., 2009; Markovinić et al., 2016). Contaminated milk with vaccinia virus (VACV) during cheese production in Brazil has also been reported (Rehfeld et al., 2017). VACV is considered a zoonosis affecting cows and humans. Artisanal cheese produced with not pasteurized milk increases the chance of infection. Rehfeld et al. (2017) found that VACV remains viable after 60 days of cheese ripening at 25 °C. Meat products are also potential targets for viral contamination, giving special attention to HEV due to its zoonotic potential (Colson

et al., 2010). The target cells of the virus are hepatocytes; therefore, the greatest risk is the consumption of contaminated animals' liver. It was recently found that, even in pH 2, there were remaining infectious virus particles in fermented meat products (Wolff et al., 2020).

Fermented oyster and kimchi were associated with NoV produced with polluted water in South Korea (Park et al., 2015). NoV has high infectivity, having the ability to withstand a broad range of temperatures and high resistance to acidic conditions. These factors facilitate NoV transmission (Park et al., 2015). Bae et al. (2018) and Gagné et al. (2015) evaluated NoV survival in experimentally contaminated kimchi and sauerkraut, respectively. In extended periods of fermentation by 90 days, virus load has decreased; however, viable copies were still present at the end of the fermentation. Rotavirus A (RVA) also easily spread by polluted water or sewage. Recently, de Castro Carvalho et al. (2020) reported RVA in homemade Minas frescal cheese collected from local

markets in the city of Mariana, Brazil. This area suffered an environmental disaster in 2015 when a rupture of an ore dam adversely affected water, soil, and air quality. Even today, Mariana and other nearby cities affected by this man-caused disaster have poor sanitation conditions and contaminated mudflow.

Colombo et al. (2018) characterized airborne VP isolated from two dairies in Italy. The authors raised some considerations about the safety of cheese ripening cellars, as human viruses belonging to the *Papillomaviridae* family showed a high abundance (17%) and identity higher than 90% with human papillomavirus. Although it is normally transmitted through direct skin-to-skin contact, the authors showed that even a slight human presence is sufficient for contamination, due to papillomavirus's high stability outside the host. Proper industrial environmental and hand workers sanitization are essential to avoid plant contamination. Although fermented foods pass through manufacturing processes that can inactivate viruses, many of them still carry infectious particles in the final product. The rapid identification of pathogens and monitoring sources of contamination are extremely important, especially for traditional fermented foods and minimally processed products (MASKE et al., 2020).

RV and HEV are members of the enteric viruses group that have zoonotic patterns (Leblanc et al., 2019). RV is distributed into ten groups or species (A to J) (International Committee on Taxonomy of Viruses, 2020) and are the most frequent species in human outbreaks. RV has segmented double-stranded RNA, which favors reassortments among human and zoonotic species. RV enteritis is frequently reported in calves and piglets in livestock (Martella et al., 2010). Contamination of food by RV occurs by primary source (water or infected animals) or along the food chain by food handlers. The WHO has recently estimated that 20 HEV infection occur annually worldwide (World Health Organization WHO, 2020). HEV is a single-stranded RNA virus with four genotypes causing diseases in humans. Genotypes 1 and 2 infect only humans, mainly in undeveloped countries by contaminated water. Genotypes 3 and 4 have zoonotic patterns (infecting humans and other animals, mainly domestic pigs), and are associated with disease in industrialized countries after consumption of raw or undercooked meat from viremic animals. Genotype 3 is responsible for the majority of zoonotic episodes. Normally, HEV causes self-limited disease, but in chronic liver disease patients and pregnant women may occur fulminant hepatic failure. HEV has been detected in meat, liver, kidney, and heart, principally from domestic pigs and wild boars (Doceul et al., 2016).

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is the causative agent of the ongoing coronavirus disease pandemic, named Coronavirus Disease 2019 (COVID-19) by WHO (Sohrabi et al., 2020). The SARS-CoV-2 is primarily transmitted by human-to-human transference via droplets (Lai et al., 2020). Other transmission routes include direct contact with an infected person and indirect contact through hand-mediated viral transfer from contaminated fomites to the nose, eyes, and mouth (La Rosa et al., 2020). Although there is no evidence that SARS-CoV-2 can be transmitted by food and water ingestion, the lack of scientific evidence leads to public health concerns mainly because the virus can remain viable for days in favorable atmospheric conditions (Singhal, 2020).

Animal-to-human SARS-CoV transmission emerged through ingestion of Chinese ferret badgers, raccoon dogs, and Himalayan palm civets sold as food (Goli, 2020), representing the primary route of transmission. The most relevant animal reservoir of human MERS-CoV, for example, are dromedary camels that caused human-human infections as occurred in Saudi Arabia in 2012 (Park et al., 2018). Reusken et al. (2014) hypothesized a foodborne transmission through consumption of raw camel milk or rawmeat, as antibodies of MERS-CoV were detected in serum and milk of dromedary camel. It was demonstrated that MERS-CoV experimentally introduced in camel milk can survive for up to 72 h at 4 °C and 22 °C (van Doremalen et al., 2014). Human Coronavirus (HCoV) was also experimentally recovered from lettuce after 4 days at 4 °C with titer 1.2×10^6 (Yépez-Gómez et al., 2013). The threat of

secondary HCoV transmission through water used for food production is also hypothesized via aerosolization/fecal-oral route (Singhal, 2020).

Usually, thermal treatment at 60 °C for 30 min is sufficient to reduce SARS-CoV in free cell matrices (Goli, 2020). CoVs are also sensitive to basic and acidic pHs (Rabenau et al., 2005), but seem to be stable at 4 °C. It was demonstrated that viral infectious level declines faster at ~24 °C than at 4 °C (La Rosa et al., 2020). In addition, CoVs seem to be susceptible to chemical agents (e.g., salt and nitrates) and physical treatments (Thippareddi et al., 2020). Fermented foods are non-thermally or chemically treated and constitute a potential route of virus transmission. On the other hand, in pH around 5, SARS-CoV nucleocapsid starts to unfold and is denatured at a pH 2.7, suggesting the sensibility of SARS-CoV to pH changes (Wang et al., 2004). In numerous fermented foods reach low pH levels and, consequently, can play a fundamental role in the elimination of the virus. All of these questions are hypothetical and should be the subject to study for verification.

After production, contamination still can occur at processing and during handling and delivery of food products by infected personnel via respiratory droplets, aerosols, or from contaminated equipment (Thippareddi et al., 2020). Recent SARS-CoV-2 outbreaks in food processing and food stores are highlighting the potential for employees being a source of contamination (Rizou et al., 2020). Considering the persistence of CoV on fresh food at 4 °C, the survival of SARS-CoV-2 on food packages was evaluated (Malenovská, 2020). The loss of infectivity of the virus on plastic surfaces was, on average, 0.93 log₁₀ (i.e. 83%) per day of storage at 4 °C. However, when using wipes saturated with a combination of disinfectant agents (hydrogen peroxide and didecyl-dimethyl-ammonium chloride), it decreased the viral titer still more efficiently, by 3.8 log₁₀ (99.98%). The Centre for Disease Control and Prevention (CDC) from United States of America states that COVID-19 infection from handling contaminated food packages have low-risk, however, it is recommended cleaning and disinfection (Seymour et al., 2020).

4. Current virus detection methods

The recovery of viruses from fermented foods consists of their separation from other microorganisms and suspended solids (Barrangou et al., 2002). In liquid samples, bacteriophages separation process can be performed by ultracentrifugation, followed by a filtering step to eliminate contaminants. Solid samples must be previously added in a buffer or sterile culture medium and stirred to elute the phages from the food matrix (Foschino et al., 2005). If the sample contains a low phage titer, concentration by ultracentrifugation should be performed previously. For phage propagation, the filtrate is inoculated into a culture medium containing the host cell (Bandara et al., 2012; Lu et al., 2003a). After overnight incubation, the culture is ultracentrifuged and the supernatant is filtered to remove the remaining bacteria cells. Then, the presence of phages and host range can be established by spot testing, plaque testing, or culture lysis. For classification, the most used method is the direct observation of morphology through Transmission Electron Microscopy (TEM), which despite being old, is still widely used. To a lesser extent, the PCR-based methods (e.g. RAPD, Multiplex PCR, MLST, and qPCR) and DNA analysis (DNA sequencing and RFLP) are eventually performed (Samson and Moineau, 2013).

Pathogenic viruses, differently from bacteriophages, are rarely propagated in cell-culture assays, and its presence is based mainly on genome copies detection. Due to significance of viral foodborne diseases, validated methods for viral analysis in food are increasing over the years, such as international standard method ISO 15216-1:2017 for NoV and HAV detection. Surrogates' viruses are frequently used to on pathogenic viruses' trials. Surrogate viruses share molecular characteristics with pathogenic viruses, such as size and chemical composition (Richards, 2012). Murine Norovirus-1, Feline Calicivirus, and some human virus strains, adapted to cell culture propagation (HAV strain HM-175, Human Adenovirus, RV, Enterovirus, and others), are the most

Table 2
Human pathogenic viral outbreaks associated to fermented food ingestion.

Virus	Classification	Fermented food	Location	Identification method	Disorder	Reference
TBEV	<i>Flavivirus</i>	Goat cheese	Germany	RT-qPCR	Meningitis, meningoencephalitis, or meningoencephalomyelitis	Brockmann et al. (2018)
TBEV	<i>Flavivirus</i>	Goat cheese	Austria	Sample no longer available	Meningitis, meningoencephalitis, or meningoencephalomyelitis	Holzmann et al. (2009)
TBEV	<i>Flavivirus</i>	Goat cheese	Croatia	Sample no longer available, however goats tested positive	Meningitis, meningoencephalitis, or meningoencephalomyelitis	Markovinović et al. (2016)
VACV	<i>Orthopoxvirus</i>	Minas cheese	Brazil	qPCR	Skin lesions	de Oliveira et al. (2018)
HEV	<i>Orthohepevirus</i>	<i>Figatelli</i>	Southeastern	RT-PCR	Acute and chronic hepatitis, death	Colson et al. (2010)
HEV	<i>Orthohepevirus</i>	Raw pork sausage	Netherlands	RT-qPCR	Acute and chronic hepatitis	Boxman et al. (2020)
NoV	Calciviridae	Fermented oyster	South Korea	RT-PCR	Acute gastroenteritis	Cho et al. (2016)
NoV	Calciviridae	Kimchi	South Korea	RT-PCR	Acute gastroenteritis	Park et al. (2015)
RVA	<i>Rotavirus</i>	<i>Minas frescal</i> cheese	Brazil	qPCR	Acute gastroenteritis	de Castro Carvalho et al. (2020)
NiV	<i>Henipavirus</i>	<i>Tari</i> (fermented palm sap liquor)	Bangladesh	Sample no longer available	Encephalitis and death	Hossain et al. (2016)

Tick-borne encephalitis virus: TBEV; Vaccinia virus: VACV; Hepatitis E Virus: HEV; Norovirus: NoV; Rotavirus A: RVA; Bat Nipah virus: NiV.

used in cell culture-based assay or molecular techniques coupled to cell culture (Plaque Assay, Tissue Culture Infectious Dose (TCID) and Integrated Cell Culture Quantitative PCR (ICC-et-RT-qPCR)) (Cromeans et al., 2008). However, these trials are still not available in the routine of food analysis laboratories and the use of surrogate viruses is not fully elucidated to predict pathogenic viruses (Richards, 2012).

Pathogenic viruses were found in fermented foods samples through PCR techniques [Quantitative (qPCR) and reverse transcription (RT-PCR), or the combination of both (RT-qPCR)] (Table 2). They are prominent in sensitivity and specificity, being more employed than antigen detection and serology. In the PCR assay, DNA/RNA isolated from the target virus are amplified with specific primers. In the supplemental material, we compiled an extensive list of specific primers designed to detect viral pathogens (Table S1). However, PCR does not show virus viability and, to generate selectively amplifiable primers, the target sequence is required in advance (Sekse et al., 2017). This limitation is aggravated by the fact that novel viruses can arise and the symptoms of viral diseases are very similar, making it difficult to know which virus is involved. To overcome this, Lee et al. (2018) proposed a PCR multiplex reverse transcription using six primer sets to simultaneously detect and quantify NoV, HAV, RV, and astrovirus in food samples (lettuce, oysters, and vegetable products). Considering the aforementioned barriers, fast and more generalized techniques for identifying pathogenic viruses are required.

5. Food virome

Great effort over the last years has been done to prevent virus contamination during fermentation processes (Park et al., 2011). However, surprisingly, viral presence started to be more noticed with the advancement of NGS technologies, and it was reframed in the fermented food niche. This transition was decelerated because food microbiome investigations are mainly focused on the characterization of bacterial and fungal communities, being virus largely neglected (Ledormand et al., 2020).

The challenges of using NGS to characterize viral content are numerous, including the absence of universal marker genes (Eric Wommack et al., 2012), the low concentration of viral DNA for preparation of genomic libraries (Garmaeva et al., 2019), the contamination of the sample with bacterial and fungal DNA (Kim and Bae, 2011), and the scarcity of databases for virus sequences as they remain largely unknown (Bikel et al., 2015; Garmaeva et al., 2019). Nevertheless, some food microbiome studies have detected, but not classified viruses in fermented food systems (Liu et al., 2020; Lyu et al., 2013). To a lesser extent, some studies have achieved a classification, even though it was focused on bacterial and fungal communities (Agyirifo et al., 2019;

Illegheems et al., 2012; Kumar et al., 2019).

Kumar et al. (2019) analyzed kinema (traditional fermented soybean from Himalaya) samples using Illumina NGS technology, and found less than 1% of total reads belonging to bacteriophages, with *Siphoviridae* family being dominant. Illegheems et al. (2012) and Agyirifo et al. (2019) analyzed cocoa beans by Illumina and reported 0,25 and 1%, respectively, of the total metagenomics read sequences being bacteriophages. Both studies reported *Lactobacillus* phages of *Siphoviridae* family as the dominant, and the presence of phages infecting *Enterobacter*, *Klebsiella*, *Pseudomonas*, *Bacillus*, and *Staphylococcus*. Interestingly, Agyirifo et al. (2019) attributed *Lactobacillus* bacteriophages to positively influence the aroma formation during cocoa beans fermentation. The authors mentioned that bacterial cell lysis caused by phages releases intracellular enzymes in the food matrix, degrading the substrate, and stimulating aroma production.

Currently, there are two approaches for metagenomic studies; i) metagenomic amplification of the target gene, where only a specific region is sequenced, performed to characterize mainly bacterial and fungal communities, and ii) shotgun metagenomics which consists of the sequencing of random fragments of all microbial DNA present in a given sample, frequently used in viral communities' studies (Sharpton, 2014). In any case, due to these advances, the terms "ome" and "omics" have been attributed to viruses.

The "virome" and the (meta) viromics refer to all viruses present in each sample and the study of their genomes, respectively (Garmaeva et al., 2019). However, since the vast majority of existing phages belong to the *Caudovirales* order, current studies on viral communities in fermented foods are strictly focused on the presence of dsDNA phages, unfortunately excluding the possibility of identifying other viruses and RNA-containing phages (Mokili et al., 2012). Most pathogenic viruses associated with fermented foods, due to their RNA genetic material content, cannot be identified by next-generation approaches. However, when associated with PCR, seems to be a promising tool for food safety monitoring. Metabarcoding strategy after RT-qPCR sample treatment has successfully been used, despite being limited to closely related viruses or viral families (Desdouts et al., 2020). If food is contaminated by innumerable viral strains belonging to different genotypes, PCR products are synthesized for each strain, and bioinformatics analyses each reading and classifies genotypes. Imamura et al. (2017) used PCR primers targeting the N-terminal area of the VP1 protein and analyzed the diversity of NoV genogroups I and II in naturally contaminated oysters with Illumina platform. Oshiki et al. (2018) combined a microfluidic tool allowing the use of multiplex PCR and Miseq sequencing to the detection of 11 different human RNA viruses from human feces, sewage, and oysters artificially contaminated. Even so, these techniques require more studies to attend to fermented foods, whereas they have

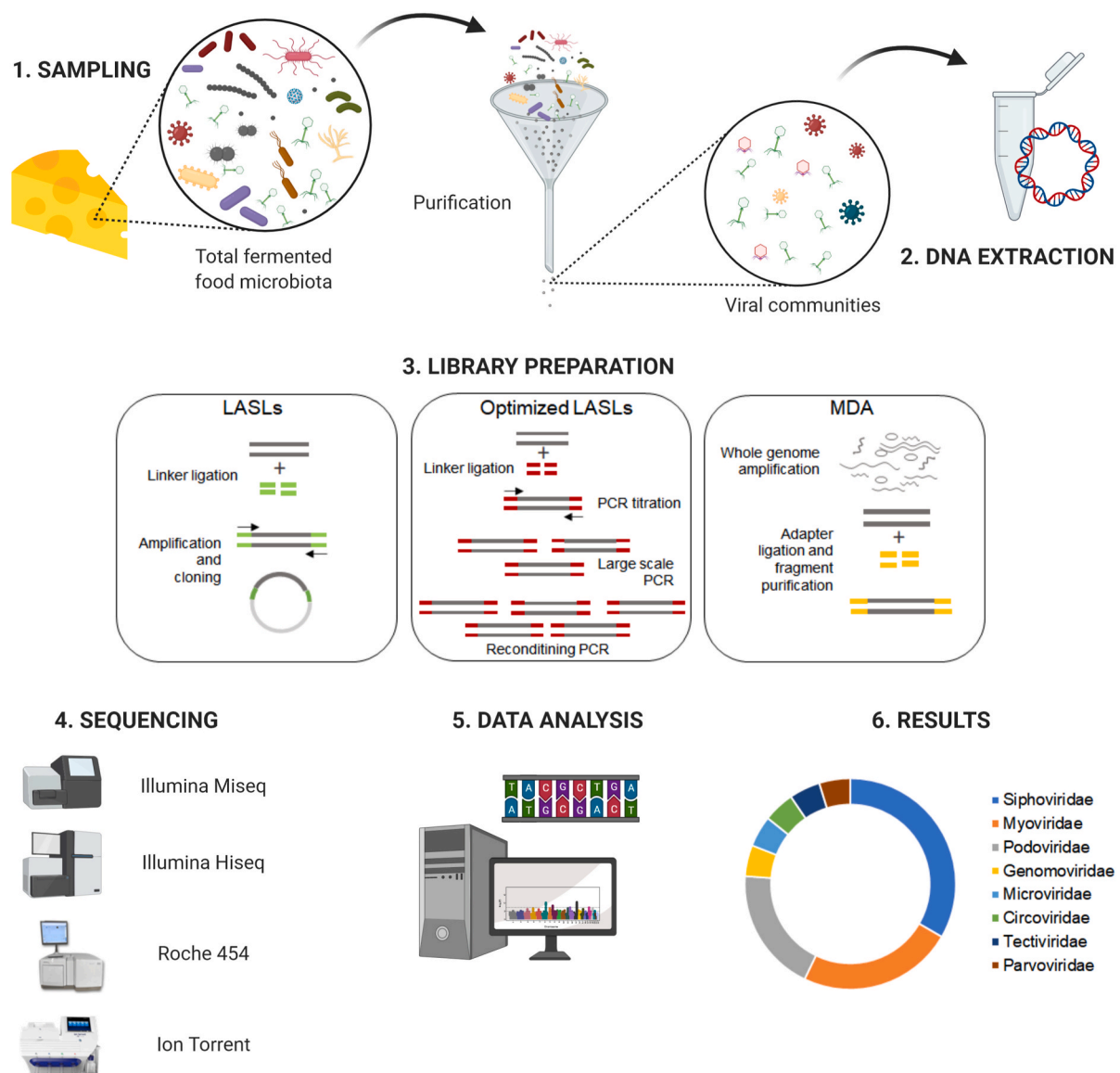


Fig. 2. Schematic workflow for analyzing virus communities in fermented foods by next-generation sequencing. LASLs (linker amplification shotgun libraries) and MDA (multiple displacement amplification). This figure was created using BioRender (<https://biorender.com/>).

peculiar characteristics affecting viral content access.

Alternatively to the term “virome”, studies of the viral community are called frequently by “phageome” (Ledormand et al., 2020). Fig. 2 illustrates the NGS standard workflow for viral community analysis in fermented foods, including (1) sampling, (2) DNA extraction, (3) library preparation, (4) sequencing, (5) data analysis, and (6) results.

5.1. Sampling and DNA extraction

All virome study starts with the step of sample purification. The purification method must be able to satisfactorily represent the original virus population (Hayes et al., 2017). Usually, the purification of the viral particles (VPs) has divided into three steps: i) VPs recovery, ii) VPs purification and concentration, and iii) an optional second purification via cesium chloride gradient (Park et al., 2011). Although there is no standardized sampling protocol for all fermented foods, recently, Dugat-Bony et al. (2020) optimized a method for extraction and purification of bacteriophages from feces to perform, for the first time, viral metagenomic analysis of cheese surface. They used a chloroform treatment and a filtration step to extract viral DNA prior to the Illumina

Miseq sequencing.

Virome studies of other fermented foods (e.g., kimchi, sauerkraut, and fermented shrimp) have used different strategies, mainly in the VPs concentration step. While Park et al. (2011) used ultracentrifuged at 100,000×g for 4 h at 4°C, Jung et al. (2018) opted to precipitate the VPs with polyethylene glycol 8000 e NaCl 1 M. In addition, due to the high concentration of cellular microorganisms in fermented food, samples are prone to contamination by bacteria. An alternative is the treatment of concentrated VPs with lysozyme and chloroform, followed by incubation with DNase and RNase to remove the remaining genetic material (Dugat-Bony et al., 2020; Jung et al., 2018; Park et al., 2011). Regardless of which purification technique is employed, a step of eliminating bacteria and fungi also means eliminating prophages that are frequently inserted in the genome of these hosts, generating a bias for the technique, as it considers only the free phage (Sausset et al., 2020).

Nevertheless, subsequently, the extraction of DNA from the VPs is performed with commercial kits. It is important to note that the choice of extraction kit influences the composition of the microbial community produced by NGS and may generate inaccurate results. Therefore, the extraction method should be chosen according to the objective of the

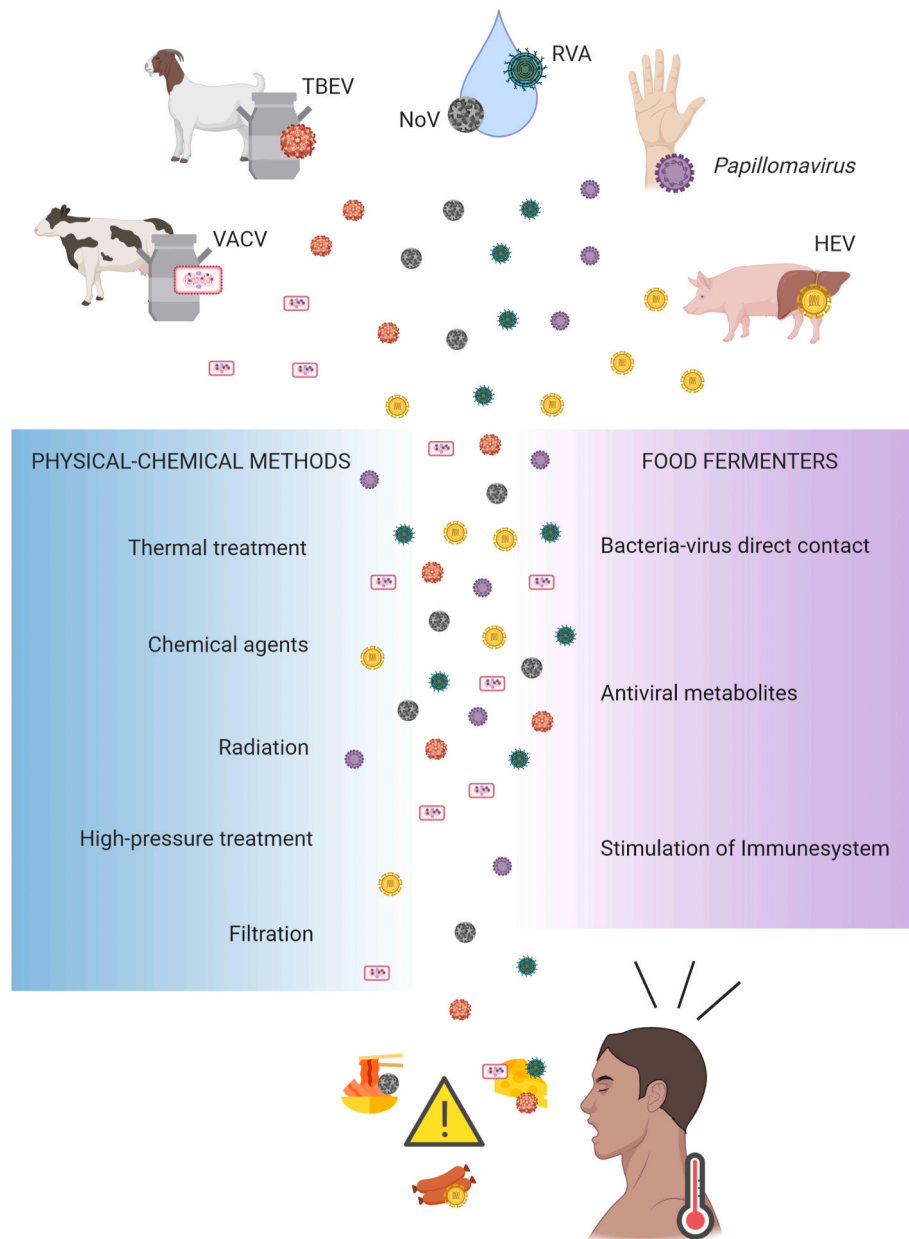


Fig. 3. Main sources of pathogenic viruses and prevention measures associated with fermented foods. VACV (vaccinia virus); TBVE (tick-borne encephalitis virus); NoV (Norovirus); HEV (hepatitis E virus); RVA (rotavirus A). This figure was created using BioRender (<https://biorender.com/>).

researcher. Also, it is recommended that after viral DNA extraction a small aliquot should be amplified by PCR using 16S/18S rRNA primers to ensure the absence of bacteria and fungi DNA contamination (Hurwitz et al., 2016).

5.2. Library preparation and sequencing

Most of the viromes that have been performed so far have used linker amplification shotgun libraries (LASLs) or whole (meta) genome amplification (WGA) methods [e.g., multiple displacement amplification (MDA)] (Willner and Hugenholtz, 2013). LASLs consist of the random fragmentation of genomic DNA and the binding of known linkers in these fragments that can be used for PCR amplification. At the time this method was developed, the fragments were cloned in plasmid vectors and sequenced by the Sanger method to generate the viral metagenomes. However, this strategy had the bias of large-scale cloning and sequencing (Breitbart et al., 2002).

NGS technologies eliminated the need for cloning vectors and significantly increased the sequencing capacity; however, the low viral DNA concentration remains a challenge since some NGS protocols require nucleic acid micrograms. Duhaime et al. (2012) optimized the LASLs technique with the addition of a titration step, significantly reducing the number of cycles and the DNA concentration required to build the library (only 1 pg), enabling large scale PCR (Willner and Hugenholtz, 2013). The optimized linker amplification (LA) technique has been adapted for 454 sequencing, but also can be used to build genomic libraries on other sequencing platforms, such as Illumina and Ion Torrent (Duhaime et al., 2012).

The MDA method uses the high efficiency of polymerase ϕ 29 which synthesizes >70,000 nucleotides per cycle from small concentrations of DNA, allowing the amplification of complete viral genomes through adapter ligations followed by purification step (Bikel et al., 2015). LA and MDA are powerful tools for studying virome, however, MDA is prone to unevenly amplify linear genome fragments and might generate

biases into the representation of ssDNA circular viruses (Kim and Bae, 2011), while A-LA provides a more reliable representation of ssDNA and dsDNA viruses (Roux et al., 2016).

After the construction of the genomic libraries, the sequencing is performed using mainly the Illumina, Roche 454, and Ion Torrent platforms (Hayes et al., 2017). The quality control steps of the generated sequences must be performed as reviewed by Hurwitz et al. (2016). Succinctly, quality control consists of ensuring optimal sequencing coverage for each sample and removing rare reads that may occur from sequencing errors or contamination of the sample, leading to overestimation of the virome diversity (Hurwitz et al., 2016).

5.3. Data analysis

The central challenge in bioinformatics analysis of viromes is the absence of universal genes, which makes diversity estimation difficult. Currently, taxonomic classification is often performed by aligning the generated sequences against a “generalist” database using the BLAST (Basic Local Alignment Search Tool) or BLAST-based programs, such as MetaPhyler (Liu et al., 2011), CARMA (Gerlach et al., 2009), and MG-RAST (MetaGenomic-Rapid Annotation using Subsystem Technology) (Glass et al., 2010). However, a large part (about 60–99%) of the sequences produced in viromes has no homology with viral sequences available in the databases.

To solve this problem, database focused on the taxonomic classification of viruses [ACLAME (Leplae et al., 2009) and Phage SEED (Overbeek et al., 2005)] and specific data analysis programs [VIROME (Viral Informatics Resource for Metagenome Exploration) (Eric Wommack et al., 2012), VMGAP (Viral MetaGenome Annotation Pipeline) (Lorenzi et al., 2011), and Metavir (Roux et al., 2014)], were developed. Usually, these pipelines use an ORF (open reading frame) localization algorithm and perform a comparison with a protein database (Hayes et al., 2017) creating a functional and taxonomic profile of the viral community (Bikel et al., 2015). In addition, an independent method of similarity PHACCS (PHAge Communities from Contig Spectrum) software was developed to better understand the structure of the viral community. It provides the estimation of diversity and uniformity revealing the most abundant viruses in a viral metagenome. This analysis is based on the principle that the most abundant virotypes in a VPs sample will more likely be assembled into large contigs (Reyes et al., 2012).

5.4. Results

The diversity revealed by virome studies in fermented foods agrees with previous findings described by culture-dependent methods. Most of the sequences belong to *Caudovirales* order of the families *Siphoviridae*, *Myoviridae*, and *Podoviridae* (Agyirifo et al., 2019; Cheng et al., 2018; Del Rio et al., 2019; Illegheems et al., 2012; Jung et al., 2018; Kot et al., 2014; Kumar et al., 2019; Park et al., 2011). Similar results are seen on the human gut virome (Garmaeva et al., 2019).

Park et al. (2011) applied pyrosequencing on fermented sauerkraut, kimchi, and shrimp samples and verified that *Siphoviridae* dominated sauerkraut (60.07%) and fermented shrimp (53.55%), differently from kimchi, which *Podoviridae* prevailed (52.82%). They also first identified *Phyconaviridae* in a fermented food, an attacker of harmful eukaryotic algae responsible for algal blooms, demonstrating that metagenomics studies contribute to the discovery of biocontrol agents for different fields other than food. Jung et al. (2018) described the dominance of ssDNA viruses in Korean kimchi, including *Circoviridae* (hosts: birds and pigs), *Genomoviridae* (plants and fungi) and *Microviridae* (bacteria), not previously described. They applied Illumina HiSeq to differentiate Chinese and Korean kimchi origins and found that viral clusters were more clearly distinguished than bacterial clusters by beta diversity analysis, making viruses more strongly associated with the geographic origins of fermented foods than the bacterial ones. The origin of traditional food

reveals its quality and safety, being of great importance to consumers.

6. Beneficial viruses: the other side of the coin

Phages directly control bacterial dynamics, promoting their balance in fermentation. In the ecological study of sauerkraut fermentation, Lu et al. (2003b) observed that the succession of bacteria was associated with the content of the respective phages found in different stages of fermentation. At the beginning of the process, *Leuconostoc* spp. and *Weissella* spp. prevailed and the phages that infected these species were isolated. After seven days, *Lactobacillus* was the main genus, and phages infecting them were observed. Recently, Kumar et al. (2019) also noticed that phages seem to determine the abundance of bacterial communities during the fermentation of Kinema, acting in the biocontrol of *Bacillus*, *Staphylococcus*, *Enterococcus*, *Lactococcus*, and *Streptococcus*.

These results suggest that phage dynamics during fermentation is crucial to guarantee a good succession of bacteria. In addition, phages can move between different environments, elevating horizontal gene transfer (HGT) and, therefore, forcing bacteria to evolve (Breitbart and Rohwer, 2005). Understand the process of phage-bacteria evolution assists the selection of good strategies to control harmful phages and maintain beneficial ones, improving fermentation performance.

Phages can act as biocontrol agents combating pathogenic and deteriorating bacteria, as well as toxic metabolic components in fermented foods (García et al., 2008). Bandara et al. (2012) found two phages belonging to *Myoviridae* family were capable of eradicating *Bacillus cereus* quickly when supplemented with divalent cations (Ca^{2+} , Mg^{2+} or Mn^{2+}) in *cheonggukjang*, a product of fermented soybean mass. Philippe et al. (2018) found a phage that infects *Gluconobacter cerinus*, a spoilage acetic acid bacterium in the wine making process. *G. cerinus* produces ethyl alcohol and transform it into acetic acid, representing hazardous to the final product. Additionally, phages can also combat toxic metabolic components released by LAB in fermented foods (Del Rio et al., 2019; Ladero et al., 2016). Recently, Del Rio et al. (2019) proved the efficiency of an *Enterococcus faecalis* bacteriophage of *Myoviridae* family in reducing biological amines (BA) in an experimental model of cheese. Phage presence reduced BA and putrescine without devastation the starter culture due to its specificity for *E. faecalis*.

The discovery of other perspectives for phages that infect LAB was also enabled. Phages that attack *Streptococcus thermophilus* were associated for decades as the cause of defects and flaws in the yogurt fermentation process (Bendadis et al., 1990; Brussow et al., 1994; Ishlimova et al., 2012; Ma et al., 2014; Quiberoni et al., 2003). However, recently, Pacini and Ruggiero (2019) attributed a probiotic potential to fermented milk and colostrum after analyzing the genomes of innumerable *Streptococcus* and *Lactococcus*'s phages contained in the product using Axiom Microbiome Array. When ingested with food, phages can influence the host in three ways: i) modulation of the gastrointestinal microbiota, as they can act against pathogens and, by promoting horizontal transfer of genetic material, it operates in the improvement and evolution of bacterial community diversity; ii) intestinal mucosa cell interaction, indirectly triggering immune system response; and iii) immune system components interaction, directly driving immune response, as they can overcome anatomical and physiological barriers, being found in compartments of the human body earlier considered sterile (Sausset et al., 2020). In this way, *Lactococcus* and *Streptococcus* phages can possess antimicrobial, antitumor, and antiviral effects on the host. In addition, phages may interact with the immune system, opening possibility to immunotherapies to treat diseases such as cancer and autism. Phages presence can enhance notable benefits, which are still untapped.

7. Final considerations

The worldwide emergence of COVID-19 resulted in abrupt awareness

of the presence of viruses in all sectors of the economy. Cases of NoVs, RVs, and HV have been reported in association with cheeses, sausages, fermented vegetables, and fermented cereals. However, there is no evidence of COVID-19 transmission through fermented foods. The possibility of food transmission needs to be investigated and clarified since no food virome study has been conducted since the first case identified in China, in December 2019. Studies have reported that Coronaviruses can remain infectious in waters and are highly stable at 4 °C, the main raw material, and storage temperature, respectively, of fermented foods. While respiratory droplets are the main way the virus spreads, transmission via fermented foods is considered negligible. However, transmission appears to be possible if the virus is transferred from hands to food and the food itself to the mucous membranes of the mouth, throat, or eyes.

A recent study showed that physical contact and shared food during a conference in Singapore resulted in a cluster of COVID-19 patients (Pung et al., 2020). The major risk enhancing factors of fermented foods is the use of contaminated raw materials, the conduction of poorly controlled natural fermentation, and the lack of pasteurization. Thus, to minimize the risk of virus contagion, good hygiene practices and cleaning of the fermentation room (taps, door handles, fermentation vessels, and utensils) should be followed by hand washing or using hand sanitizer.

On the other side of the coin, emerging evidence of bacteriophages diversity in fermented foods by NGS has revealed an ongoing paradigm in understanding their role in this ecosystem. The positive influence of phage is ample, ranging from sensorial improvement of the fermentation process to probiotic potential by cell interaction. To overcome unexplored fermented food viromes ecosystems, current challenges, such as the expansion of databases for non-cultivable viruses, the optimization of isolation protocols, and new bioinformatics tools, demands to be faced. Establishing viromes of innumerable fermented foods, studying the long-term evolution of virus-bacterial interactions, analyzing the influence of external factors, and elucidating the interaction of viruses with consumer's gastrointestinal tract cells will be essential in keeping viruses as allies.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fm.2021.103794>.

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