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STRATAGIES USED TO CONTROL BACTERIOPHAGES CONTAMINATION IN DAIRY FOOD AND INDUSTRY

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Abstract

Bacteriophages are the most important cause of fermentation failure in the dairy industry because they are present normally in the environment. These mostly infect Streptococcus thermophilus, Lactococcus lactis, and Lactobacillus delbrueckii species. Phages spoils the dairy products; thus, it should be removed from industry to obtain good quality products. This review focuses on the main sources of contamination and strategies to control phage infection in dairy industry. These include factory design, control of air flow, use of sanitizers, restricted used of recycled products, selection and growth of bacterial cultures, starter rotation, selected media and products organization can limit the number of phages to some extent. Phages are also hazardous for yogurt processing and for this, 3-component yogurt starter were designed to stabilize and improved fermentation process in the presence of phages. Another food refining treatment is the use of live microorganisms to stop or remove pathogenic and/or spoilage bacteria in/on food and it is bacteriophage-based treatment which focus on their mode of action when used for foods i.e., milk and dairy products. Bacteriophages infect whey sample, causes problems in cheese plant as separation of whey leads to aerosol-borne phages. Whey proteins or cream used for reprocessing may have thermo-resistant phages. To eliminate this risk, inactivation of phages by thermal treatment, ultraviolet (UV) light irradiation, membrane filtration and a combined treatment using membrane filtration or UV in combination with thermal treatment, can reduce the phage numbers and growth in whey.

Keywords: *Bacteriophages, streptococcus thermophilus, lactococcus lactis, lactobacillus delbrueckii, phage contamination sources, phage control strategies.*

INTRODUCTION

Fermentation method has been used as food conservation for 1000 years. Through microbial fermentation a wide range of food supplies are produced even today including milk products e.g., buttermilk, cheese, sour cream, and yogurt (1). Fermentation process not only enlarges the shelf life of foodstuffs but also gives new flavor and texture (2). Changes in organoleptic properties of cheese and fermented milk products and gas formation are due to fermentation fault in foodstuffs. For the fermentation of milk, the widely used starter cultures are *Lactococcus lactis* strains. In the environment of fermentation, virulent bacteriophages appear against these strains in making several types of cheeses, sour cream and buttermilk (3), thus, it is important to know the function of bacteriophage and what should be done to reduce them (4).

The most copious biological unit is the bacteriophages on earth (>10^{31}) and is 10 times more plentiful than bacteria (5). In dairy industry fermentations, bacteriophages are the main cause in world-wide as they are naturally present in the milk (6). The cause of quality failing is due to phage that changes the flavor, texture, even protection of dairy food (7). Frederick Twort and Fe´lixd'He´relle in 1915 and 1917 co-discovered the phages and their first harmful effect was reported in mid 30s of twentieth century on dairy fermentation (8). They cause low fermentation, less acid production and decreasing milk quality which results in deep economic losses (9). Failure in cheese-starter cultures in which the *Streptococci* are lysed is due to bacteriophages. Bacteria when living in unfavorable situation could themselves give rise to the phage immediately after their transfer to a fresh batch of milk (10).

Lactococcus lactis is infected by multiple species of phage. The most common phage to *Lactococcus lactis* is P008, however, normally found species in dairy factory are C2, 936, and P335. Of these species 95% cause problems in dairies and milk fermentation. The most heat resistant *Lactococcal* bacteriophage is P1532 and P680 in milk (4). Industrial problems of about 60–70% are due to bacteriophages during production of cottage and hard cheeses (3). The use of culture rotation system and mixed-strain starter cultures do not block the overall batches fermentation; however, delays in manufacturing and differences in product quality are often common (11). Due to regular progress of new phage-resistant bacterial strains and starter strain rotations, phage remains the most severe route of fermentation fault economically (12). As bacteriophages are the threat to dairy, to lessen load on factories and invent latest screening systems, a huge research attempts have been made for their initial finding (13). The turbidity/growth test and spot/plaque analysis are 2 methods most often used (14, 15) and found reducing the growth of bacteriophages in host strain (16).

For many years now the industry has been contracting with their biological occurrence and routes to control phages, which depend on various pathways such as better starter medium, modified plant design, method changes, sufficient aeration, better hygiene and culture rotation (17). Due to bacteriophages different approaches have carried out in factories to reduce danger of fermentation faults (18). One way of controlling bacteriophage is thermal treatment. In dairy products the heat resistant phages are inactivated by the combination of exact time/temperature in heat handling (19, 20). During reprocessing whey and consumption of their products (fresh cheese and yoghurt), phage removal processes are much essential, as the reuse of whey still mean the threat of phage contamination of dairy atmosphere (21).

To control bacteriophages, number of methods has been developed in which starter preparation (22) and correct starter rotation are important. Other methods are the New Zealand system (23) in which a single known strain is employed to ready starter cultures and the Netherlands system (24) in which phage in-sensitive strains are changed to commercial circumstances. For about over 70 years the dairy microbiologists have tried to remove the bacteriophages or to bring a better control (25). The purpose of this review is to focus and explain the main sources of phage contamination through which different control strategies will be used by different dairy industries to limit bacteriophage attacks.

PHAGE CONTAMINATION SOURCES

Phages can originate from various sources in dairy industries. Firstly, recognize the possible source of phage and then limit their entrance to the fermentation process. Therefore, through the sources of phage contamination a suitable phage control strategy will be applied to limit bacteriophages in dairy industry. Sources of contamination are as follows:

RAW MILK

In a factory the first source of phage entrance is raw milk. Phages of LAB in raw milk are naturally occurring at low titers (between 10^1-10^3 PFU ml ^{1}) which provide bacteriophages in industries (11). In raw milk, the concentration of phage depends on the farmer storing, assembling, and managing and carrying to the factory and lastly milk treatment itself in the plant (26). About 37% of *lactococcal* and *streptococcal* phages in the milk sample have been detected using a multiplex PCR method, used to produce yoghurt in Spain (27). Heating of milk is important up to 90˚C for yogurt formation (28), and this can eliminate most phages (29).

WHEY PROTEIN AND MILK POWDER CONCENTRATES

For yoghurt, ripen cheese and fresh cheese production, milk powder is used in several countries. Earlier fermentation process, to get better final product consistency and flavor and nutrient, whey proteins are utilized to normalize milk (20). Recycling of whey protein concentrates (WPC) is to enhance the product yield or quality of end product (30) but this process is unsafe because of the presence of phages in these elements (31). Thus, these concentrates are the cause of extreme heat resistant phages that can affect the value of product (20). By ultrafiltration and/or microfiltration to separate whey components, it is possible that phages will be maintained when using membranes (32).

STARTER CULTURES AS A RESERVOIR

When strains have moderate phages then starter culture became a resource of phages. When it penetrates a strain, it incorporates its genome into the bacterial chromosome and begins reproduction. Prophage can be activated and start lytic cycle indifferent bacterial stresses e.g., temperature, salt, antimicrobials, malnourishment, or UV (33). New research discovered that out of 30, 25 profitable or dairy separated *Lactobacillus paracasei, Lactobacillus rhamnosus, Lactobacillus casei,* were found to activate prophage (34). The use of prophage-cured strains or selected strains that cannot be activated under stress state is to avoid cell lysis and viral variety in the production process (35).

EQUIPMENTS

` The most possible sources of virulent phages in dairy factory are equipments. On working bench phages are normally present. The serious phage problem is the creation of biofilms on dairy equipment's (36). These were noticed on pipelines, walls, ground, doorknobs, and staff tables and on cleaning equipment's found in cheese plants. Handling of cheese milk, raw milk and whey produced in unlock containers can cause phage dispersal in the air (36). Thus, fermentation equipment's and tools must be carefully cleaned and sterile to reduce the risk of phage contamination.

AEROSOLS

Another source of phage's contamination is aerosols and an important path of spreading (37). The steps of cheese production and whey separation giving rise to the most of aerosols (38). Neve *et al*., 2003 found higher phages concentration near the whey separator, when reviewed the airborne phages in cheese plant. Staff movements or raw material and equipment's transport may be the reason of dispersal of aerosol containing particles of phages (37). Hence, these phage contamination sources will speak about proper phage control strategies.

PHAGE CONTROL STRATEGIES

Phages quickly spread and are hard to remove in dairy environment. Microbiologists have tried to eradicate or to bring better control of bacteriophage for about 80 years because they are at continuous risk of financial losses in the dairy production. Many difficult methods have been discovered above last ten years to defeat phage populations within dairy industry. Their existence in the fermentation is more likely to plan for well-organized control strategies instead of fully removing them. Following are the important procedures for phage control in dairy products and will help reducing the risks of fermentation failure (25).

PHAGE CONTROL IN DAIRY PRODUCTS

CONTROL OF PHAGE IN MILK

Milk elements possibly contain LAB virulent phages which should be treated to overcome viral load. The most common process in dairy industry to lessen the spoilage of product and microbial growth is milk pasteurization (13). But in normal pasteurization some phages remain active (19). To defeat phage risk, thermal treatment can enhance the safety of fermentation method. Another process is Ultrafiltration (UF), in which the molecules are retained of a certain molecular weight. During milk UF, all proteins are retained, as bacteriophage proteins have molecular weights of 23,000 to 77,000 (39), thus, phages in milk would be retained and this showed that phage do not pass through the membrane (40).

Other method is the use of various types of phosphates, i.e., orthophosphate, metaphosphates, tripolyphosphates, and pyrophosphates; these are added to milk to know their effect on phage propagation. Orthophosphates are more useful than others and has less inhibitory effect on lactic culture activity. Tripolyphosphates and pyrophosphates are tested separately and are unsuccessful against phage but enhance the efficacy of orthophosphate treatment (41). Milk treated with orthophosphate, by the addition of pyrophosphates did not reduce the unbound calcium but actively repress bacteriophage growth; hence, it cleared the pyrophosphate role in milk preventing phage propagation by complexing other divalent metals. Thus, this showed that the adsorption of phage to the host cell is greatly weakened by the addition of phosphate to the milk (41).

Phages that were resistant to temperatures of 97°C for 5 min were 936-like *lactococcal* phages (19) and c2-like phages were less resistant (42). Phages that are extra resistant to temperature handling are *Lactobacillus helveticus* and *Lactococcus lactis* than *Lactobacillus delbrueckii* and *Streptococcus thermophilus* phages (19). Phages depend on the shape of food (milk powder, milk, whey etc) and react differently (43). Müller-Bach and colleagues have verified that to reduce phage infectivity, high pressure and temperature show symbiotic result. Milk has a defensive effect because of the protein, whereas *lactococcal* phage resistance to heat does not increase due to the higher concentration of salt or fat (19).

Phages also play a main role in controlling pathogenic or bacterial spoilage of food. Bacteriophages have been added with the purpose knowing their effectiveness in eradicating undesirable bacteria from dairy goods. Whitman and Marshall gave the first testimony of phages for spoilage bacteria of milk (44) and recovered phages from raw skim milk i.e., *Pseudomonas fragi*. Phages could decrease number of *P. fragi* in milk (45). Ellis, *et al*., (1973), Patel, and Jackman, (1986) demonstrated that bacteriophage in milk possibly lessen the number of the *Psychrotrophic Pseudomonas*. These all show that by adding bacteriophages can eradicate pathogenic and unwanted bacteria from milk and dairy goods (45, 46).

Control of Phages in Yoghurt

Yogurt is formed by varied starter cultures containing *Lactobacillus delbrueckii* ssp. *Bulgaricus* and *Streptococcus thermophilus* (47). In yoghurt, *S. thermophilus* is involved in the production of exopolysaccharide (EPS) (48) and rapid acidification (49), but to show all the features for manufacturing a good product, it is hard for only *S. thermophilus* strain. Thus, Skriver, *et al*., (2003) explained an idea of starter cultures, mixing *L.bulgaricus* strain and 2 *S.thermophilus* strains and this mixture of strains hypothetically, fuses the benefits of good smell, reduced fermentation time and fine texture if EPS-producing, odor-producing, and quick acidification (50).

In dairy environments, phages nearly survive everywhere which is a universal problem and causes low-grade quality products and slowed fermentation (51). Thus, it is vital to defeat phage infection and improve the fermentation process by building up excellent yogurt starter designs. Decrease in EPS formation and acidification is due to phage-resistant *S. Thermophilus* (52). The strategy used for this issue is the use of insensitive and sensitive strains of *S.thermophilus* joint with *L.bulgaricus* strain to make up a 3-component yogurt starter. In the presence of phages, the 3-component yoghurt starter was examined in turn to reorganize the design and utilization of the yogurt starter (53) in fermentation process.

Phage infection delayed fermentation by using 2-component yogurt starter i.e., sensitive strain of *S.thermophilus* with *L.bulgaricus* strain (53). Phages reduced the mouth thickness, creaminess and effect ropy of yoghurt by using 2-component yogurt starters, living cell counts of *S.thermophilus* reduced fast, yogurt appeared to be rough and grainy and diminish EPS production due to phage attack (54). In 3-component starter, insensitive strain could grow and proliferate whereas phages only repressed the development of sensitive strain. Thus, multicomponent yogurt starters along with phages improved fermentation and maintained the process (53).

Control of Phage in Cheese

Phages in the biosphere, spoils the taste and thickness of cheese. In one slice of cheese about one billion phages are found (11). The reprocessing of whey element (i.e., whey cream& whey proteins), their absorption onto cheese milk in current cheese production is normally done to enhance financial and nutrient value of cheese making (55). Phages in cheese making leads to slow down the fermentation process or might stop it which results in reduced the ability of acid production or poor value of low acid cheese (11). Bacteriophages that contaminate the whey samples cause problem in cheese plant because the separation of whey directs aerosol-borne phages and contaminate the environment (56). The starter cultures that are assaulted by heat resistant phage are mesophilic and thermophilic cultures used in the manufacturing of mozzarella, semi-hard and hard cheeses (67). During cheese making, phage in cheese whey is the main cause of phage infection.

For phage controlling, modern methods used in cheese making are use of starters having phage-insensitive or phage-unrelated strains, making of phage-free size starter, reducing phage in processing plants by air conditioning, aerosol production/disinfectant, culture rotations, cleaning/chlorination of containers between refills, site of whey storage reservoir, whey treatment systems and excellent factory design. For the formation of phage-free size starter professionally qualified, expert staff and different apparatus are needed. Those factories that do not have sources to make phage-free size starter, for them adding of concentrated starter cultures to the cheese-milk is a main control method (58).

In other studies, bacteriophages are useful to eradicate pathogenic and unwanted bacteria from dairy goods. In the production and preservation of cheddar cheese, Modi and co-workers described the reaction of phages on the survival of *Salmonella Enteritidis.* He said by adding anti-*Salmonella* to cheese milk, can decrease the amount of *Salmonella Enteritidis* in cheese prepared from raw and pasteurised milk (59). In many dairy goods, *Listeria monocytogenes* is another problem, especially of raw-milk cheeses and this pathogen was completely removed from the soft cheese (60) and mozzarella cheese (61) by the treatment with anti-*Listeria* bacteriophage (60). During cooking period of cheese production, prophage initiates the release bacteriophages into cheese curd and cooking brought the lysis of a starter culture. Feirtag and McKay established the concurrent discovery of bacteriophage particles by electron microscope (62).

Control of Phage in Whey

Whey is often recycled from the previous cheese bunch to better the quality, enhance nutrient value of end product and raise the yield in cheese manufacturing industry. Whey cream and unrefined proteins is reprocessing on regular basis, but majority of bacteriophages re-enter the cheese production which tolerate pasteurization and increases the risk of multiplication of phages to higher number (56), whereas the used whey of cheese is usually infected by phages (19, 20). The thermo-resistant phages are prevalent in dairies and exist in normal phage inhabitants shown by Atamer, *et al*., (2009). The major cause of contamination in dairies is the raw milk that is infected by phages 10^4 ml^{-1} (63) and their number in whey increases as high as 10^9 $PFUml^{-1}$ (19, 20) causes the phages eradication more complicated (56).

The removal of risk of fermentation stoppage and inactivation of phages during whey reprocessing is via ultraviolet (UV) light irradiation, membrane filtration and thermal treatment. Using UV treatment or membrane filtration in fusion with thermal treatment, the number of phages can be decreased to stop growth of following phage in whey (56). Following are the heat treatment processes used to eliminate phages from whey.

Inactivation and Thermal Treatment of Phages in Whey

Thermal procedure is used to inactivate the toxic wastes and left-over starter bacteria into cheese milk (whey cream and whey protein particles) before reprocessing. In dairy atmosphere and in milk goods, the appearance of phages may occur due to insufficient heating of whey. The existence of heat-resistant phages after reprocessing of whey, heat treatment guaranteed 9-log reduction of phages to remove the risk of fermentation fault (64). Heat treatment with mixture of harsh temperature/time, affect the properties of the product, thus non-thermal processes are also applicable for removal of phages (56).

UV Treatment in Whey

UV treatment is an alternative of thermal treatment, a strong method used for inactivation of microbes and for sanitizing drinking water, surfaces and wastewater (65). UV treatment have some restrictions as it cannot enter cloudy solution, thus a new technique, the UVivatec® method makes the use of UV to penetrate very cloudy solution. In reprocessing of whey, UV method may be used in future for the inactivation of bacteriophages (56).

Membrane Filtration of Phages in Whey

In dairy industry, microfiltration processes are extensively used. Membranes are used to separate the microorganisms in milk and segregate floating particles with pore size about 1μm (66). Membrane pore sizes may vary for whey protein parts and milk proteins fractions into casein i.e., from 0.05 - 0.2μm. From whey, the partition of microorganisms and inorganic materials result in making of layer on the membrane. Thus, membrane filtration method helps to observe the dairy phages separated from whey by means of preventing whey protein denaturation (56).

Collective Treatments of Phage in Whey Products

Phages that are heat-resistant are neither eradicated via high temperature/short time (HTST) nor by low temperature/longtime (LTLT) pasteurization. Hence, it is suggested to combine various methods of inactivation (combination of thermal and non-thermal methods), instead of implementing individually. Multiplication of phage on membrane filtration can be stopped by isolation of host cell of lactic acid bacteria. Membrane with pore size about 100 nm contains both some phages and LAB while some much smaller whey protein (i.e., α-lactalbumin and β-lactoglobulin) pass through microfiltration (56).

PHAGE CONTROL IN DAIRY INDUSTRY

Sanitization Strategy

The first step in dairy production is to clean industrialized conveniences, as infectivity of phage is verified. The disinfecting chemicals should be chosen for the industry, as their usefulness is afflicted by contamination. Sanitizing methods such as heat, alkaline (pH 11 & higher) and acidic handling (pH 4 &lower) are most effective against phages and for utensils used in dairy plant. The most effective biocide is peracetic acid, less efficient is ethanol and isopropanol whereas sodium hypochlorite is effective against LAB phages but had a changeable effect (13). Except peracetic acid all the other three are used for cleaning surfaces and equipment's of laboratory and less efficient against inactivation of phages (18). Sanitizing chemicals in the form of aerosol, liquid and foam, within 2 min inactivated 99% of phage particles in reconstituted dried skim milk. Cleaning methods is to retain phage at low level, reduce the risk of their distribution and infection within the industry (67) and remove 90% of microbes from surface but do not kill them (68).

Starter Culture and Rotation

The dairy factory after cleaning process, must choose the starter culture to start fermentation process whether by using the same one or by a new bacterial strain. Dairy plant has been rotating various starter cultures from last ten years to prevent increase of phages as well to lessen the fermentation fault (69). The use of uncertain multi strain and multispecies culture in the past was a major method to defeat phage production in several industrial units (Flora Danica-Chr. Hansen, Probat 505-Danisco). The use of 3 derivative of a single strain upon their constant rotation is a good process to defeat phages but in case of 1 strain and its deviation, partial number of strains not only restricts the phage number but also limit the occurrence of new phages in dairy industry (70). Basically, cultures rotation is an effective method for phage managing, which not only evades the same phage recontamination but also decrease the phage levels in cheese industry. This strategy is not appropriate for all industrialized procedures, but it recommends a quite easy method to reduce fermentation faults because of phages (13).

Phage Inhibitory Media (PIM)

The constant use of phage-resistant media directs the variety of phages. Thus, media for culturing should be planned to include elements that holdup/reduce spreading of phage e.g., culture media consists of chelate i.e., citrates of phosphates (71). PIM (Phage inhibitory media) is applied for phage control. To stop the attachment of phages, PIM are prepared with phosphates to chelate the calcium ions (72). Pure peptidases a stabilizer was used when the phages were inactive, to secure a culture of *Lactococcus* (73). These peptides in L-M17 medium and milk (contains phage), prolong the *Lactococcus* culture growth. Starter culture containing peptides once ready in a medium, the cultures can be defended from contamination during ripening and renneting period (67).

Elimination of air-born Phages in Commercial Practice

At present for the removal of starter malfunction caused by phage, 3 techniques are continuing experiments in profitable plants. 1. Devastation of air-borne phage by antiseptic in spray form. 2. Preservation of cultures from air-borne phage in the industrial unit. 3. Formation of the starter in an isolate building to prohibit phage loaded air. The antiseptic if efficient in any way, should be spread in extremely good condition. The large size culture processed in cans, can be protected to some level by making the cap air-tight and left a tiny hole with a cotton wool by which milk can be introduced, thus the entry of air-borne phage to the starter can be controlled to an extent. For preventive airborne phage good ventilation systems are required (37). To eliminate all air-born phage, an isolate building from the industry is a possible, well planned, and entirely acceptable method for eradicating problems (10).

Production Organization

Organization of production can lower the phage spread in dairy industry. Improvement and execution of the procedures can overcome the danger of phage in industry. To control the phages one should perform the following (25): regular analysis of phage discovery, positive pressure and air filtration (HEPA) inside fermentation tanks and manufacturing companies, fresh and sanitize walls, floor, storage bin, lines and exhaust directly used once the system close, elude crossing paths for raw milk, use steam sanitization for manufacturing row mainly when contamination is high, evade use of similar apparatus for whey and raw milk carrying & handling, isolate packaging and fermentation region, arrange torpid tract of milk, water, foam and whey from manufacturing passage or pools liquid including cultures and limit staff movements. For all this, industry must be alert with significance of control of phage hazard, well familiar by the techniques and follow them (68).

CONCLUSION AND FUTURE PERSPECTIVE

This review has explained that bacteriophages cause contamination in dairy industry because they are widespread in the environment. Researchers after conducting different experiments explained several sources of contamination and confirmed that milk being the most significant cause of phage contamination in industrial unit. Air-born phage is a common source of starter failure. Thus, various phage control strategies had been developed which largely depends on the type and size of the manufacturing facilities and to some extent can limit the phage numbers in dairy industry. Phages are eliminated by various methods including thermal treatment, starter rotation, phage inhibitory media, an adapted factory design, UV treatment, cleaning and disinfection, proper air control and product organization. To eradicate phages from air & apparatus, raw materials & by-products novel tools are still desired. Complete elimination of phages is not achievable at the present time; good manufacturing practices and well-trained staff will ensure good control of phage population. Modified phage inhabitants are continuously developing and arising within a factory over time; therefore, control strategies should be periodically revisited. Hence, to control phage evolution; it is crucial to discover new antiviral approaches. Upgrading is still required to lessen the trouble related with phage infectivity. Understanding more phage variety & host relations, research branch is involved to incorporate phage techniques with the expectation to better the anti-phage methods and LAB strain selection route in future. To confirm that phage sterilize methods are simply accessible, functional and safe, it is essential to perform more research and evolve proper control methodologies for future perspectives.

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Abbreviations

LAB: lactic acid bacteria; UF: Ultrafiltration, ESP: Exopolysaccharide's production, PFU: plaque-forming unit, UV: ultraviolet, PIM: Phage inhibitory media, WPC: whey protein concentrates, PCR: polymerase chain reaction, HTST: high temperature/short time, LTLT: low temperature/longtime, HEPA: high efficiency particulate air

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