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Wonder World of Phages: Potential Biocontrol Agents Safeguarding Biosphere and Health of Animals and Humans- Current Scenario and Perspectives

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Abstract: Darwin's theory of natural selection and concept of survival of fittest of Wallace is a universal truth which derives the force of life among all live entities on this biosphere. Issues regarding food safety along with increased drug resistance and emerging zoonotic infections have proved that multidisciplinary efforts are in demand for human and animal welfare. This has led to development of various novel therapies the list of which remains incomplete without mentioning about phages. Homologous and non-homologous recombination along with point mutation and addition of new genes play role in their evolution. The rapid emergence of the antibiotic resistant strains of bacteria have created keen interest in finding necessary alternatives to check microbial infections and there comes the importance of phages. Phages kill the bacteria either by lysis or by releasing holins. Bacteriophages; the viruses that live on bacteria are nowadays considered as the best biocontrol agents. They are used as replacers of antibiotics; food industry promoter; guard of aquatic life as well as of plants; pre-slaughter treatment agents; Generally Recognized As Safe (GRAS) food additives; Typing agent of bacteria; active tool of super bug therapy; in post harvest crops and food and during post infection and also to combat intracellular pathogens viz. Mycobacteria and Mycoplasma. Cyanophages/phycophages are particularly useful in controlling blooms produced by various genera of algae and cyanobacteria. By performing centrifugation studies and based on electron microscopy certain virus like particles containing ds RNA have been confirmed as mycophages. They are well proven as threat to pathogenic fungi (both fungal hyphae and yeast). Those that infect yeasts are called zymophages. Virophages have exquisite specificity for their viral host, hence can extensively be used for genetic studies and can also act as evolutionary link. After the discovery of very first virophage till now, a total of 3 virophages have been discovered including the Sputnik virophages that are used to study genetic recombination. Virophages also find their application in antiviral therapy; as engineer of ecological system etc. In brief, present review deals with various dimensions of these beneficial viruses that are being used and can be successfully used in future for safeguarding biosphere including animal and human health.

Key words: Bacteriophage, cyanophage, mycophage, virophage, pathogen, animal, human, antiviral, antibacterial, antifungal, food safety, therapeutic, treatment, biocontrol

INTRODUCTION

Since the origin of life on this planet, a race between all the living forms for the survival is continuing. Darwin's theory of natural selection and concept of survival of fittest of Wallace is a universal truth which derives the force of life among all live entities on this biosphere. From the time of evolution, enormous types of species are being originated, prokaryote to eukaryote, unicellular to multicellular, all are living together in an ecosystem by maintaining various types of community relationship viz, independent, synergism, mutualistic, symbiotic,

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parasitic etc. In this mysterious world of various life forms many agents are infectious also, which have ability to harm other organisms by exploiting them either by deriving nutrition or energy for their survival. To achieve the protection against these invaders, higher life forms have developed special kind of defense mechanism in order to avoid any deviation or alteration from normal physiology. This natural defense system is affected by various internal and external, specific or non-specific, environmental and biological factors, therefore, it needs to be complemented and supported simultaneously. Issues regarding food safety along with increased drug resistance and emerging zoonotic infections like swine flu (Dhama *et al*., 2012), arcobacteriosis (Patyal *et al*., 2011), salmonellosis (Verma *et al*., 2007; 2008a; 2011a, b), foot-and-mouth disease (Verma *et al*., 2008b, 2012), marek's disease (Singh *et al*., 2012), mycoplasmosis (Kumar *et al*., 2011), campylobacteriosis (Kumar *et al*., 2012), brucellosis (Kumar *et al*., 2009), listeriosis have proved that multidisciplinary efforts are required at global, national and local level for betterment of health and well being (Bender and Shulman, 2004; Dhama *et al*., 2013a). Diagnosis is considered as an integral part of war against combating killer diseases of humans and animals (Dhama *et al*., 2013b). Side by side therapeutic approaches are needed to strengthen our efforts to maintain global health (Dhama *et al*., 2013b). Their needs are felt more badly especially during the threats of pandemic viz. avian influenza or swine flu (Dhama *et al*., 2005, 2012). Since past historical time this concept was known by the health-practitioners, clinicians, biologists and that's why even at that time herbal therapy, ayurvedic science, homeo-pathy, many conventional remedial preparations were used for safe-guarding the health and life. Several novel therapies have come up as bonus due to advancement in the field of science; Molecular biology and biotechnology along with nanotechnology (Bartol *et al*., 1999; Chakravarthi and Balaji, 2010; Shirley *et al*., 2011). They include: avian egg antibody; cytokine as well as gene and apoptins; stem cells; nanomedicine and vaccines but the list remains incomplete without the mention of the space-shuttle shaped viruses, phages (Dhama *et al*., 2013c, d).

It is a well proven fact based on immense studies in the life sciences that not only human or animals but plants, fishes, insects, fungi, algae, protozoans, bacteria and even smallest infectious pathogen i e., virus may also get infected. To counteract with the infectious agents many new treatment modalities were invented and many are still in the pipeline. Discovery of antibiotic by Sir Alaxander Flemming was a great breakthrough in this battle between host and parasite/infectious agent. They had been invented as magical drugs which were acquired from certain micro-organisms and were able to subside/reduce the growth of other specific micro-organisms. But, an emergence of antibiotic resistance and multidrug resistance among disease producing bacteria in 1940's led scientists to again look for alternative potential candidates to win over infectious diseases. The emergence of multidrug resistant bacteria has become a critical problem in modern medicine. Therefore, other beneficial bacteria and viruses such as bdelovibrios or bacteriophages were found appropriate to replace the indiscriminate use of antibiotics (Wilkinson, 2001; Rhoads *et al*., 2009). In this context, present review discusses various dimensions of beneficial viruses of different species which are being used and can be successfully used in future as a strong anti-infective and promising therapeutic tool in the scenario of developing antibiotic resistance.

How phages evolved: Non-homologous recombination is not the only mechanism of evolution of phages and homologous counterpart indeed plays role in evolution of phages and occurs with a greater magnitude. Unlike non-homologous phenomenon homologous recombination however does not change the sequence at the site of recombination but bears the potential to make major changes in the phage genome causing reassortment of flanking genes and mosaic joints (Clark *et al*., 2001). Role of point mutation (Hendrix, 2002) and addition of new genes (Juhala *et al*., 2000) in the process of evolution of phages can not be ruled out.

Due to rapid emergence of antibiotic resistant strains of bacteria treatment of infectious diseases with antibiotics is becoming challenging day by day and raising bacterial resistance is becoming a matter of global concern. The natural ability of infectious bacteria to develop immunities to multiple antibiotics has become an alarming health concern particularly due to the continuous increase of immunocompromised patients (Duckworth and Gulig, 2002; Hanlon, 2007). Consequently, it is producing a growing interest in finding viable alternatives for disease prevention and growth enhancing supplements as well. The potent candidates including bacteriophages have been used as an alternative to antibiotics and attracted the attention of scientists and clinicians both, their cocktail preparation has already been in use to mitigate bacterial population and is available with various commercial names in the market also. Similarly to check fungal infections mycophages, to infect yeasts zymophages, to prevent algae from infections and thereby maintaining the biological equilibrium of ocean and ponds

phycophhages/cyanophages and even to counteract certain large sized viruses concept of virophage is also in picture (Hendrix *et al*., 1999; Hendrix *et al*., 2000).

At present very few new antimicrobials are in the pipeline of pharmaceutical industry, reason is not the scarcity of microbicidal preparations but is due to fast evolving strategies acquired by microorganisms in the changing climatic and environmental conditions. Food safety is another major issue of world concern. For safer health consumer demands healthy aquaculture/food products from farm to table. The availability of fresh foods without chemical preservatives is the need of the day and hence it is imperative to find out novel candidate, which can work without use of chemicals and drugs in order to avoid residual toxicity hazards in the food products (Oliver *et al*., 2009). This alertness among the society is opening new avenues for treating infectious disease but other approaches and biocontrol measures should also be searched out. Indeed, it is the time to explore all the hidden attributes of micro-organism and to make critical strategies to use them cleverly against infectious agents because being biological entity they will not be provoking diversified side effects. While using such micro-organisms as remedial agents there will be several multi-facets advantages over synthetic commercial preparations (Abedon *et al*., 2011).

Bacteriophage: Therapeutic conqueror of bacteria: Discovery of presence of these bacteria eater viruses in the river Ganges by Hankin supported the religious belief of being this river holy and destroyer of sins. More than a century ago, the first observation of phage-activity was recorded in India (Hankin, 1896) in the rivers Ganges and Yamuna against *Vibrio cholorae*. Marked anti-bacterial action was noticed which destroyed causative bacteria of cholera in culture and among the people who consumed the river water (Inal *et al*., 2003). At the beginning of the 20th century, almost 20 years after Hankin's observation, Twort (1915) and D'herelle (1917) reported similar filterable entities capable of destroying bacterial cultures (Twort (1915). D'herelle (1917) named these ultra microscopic, healing viruses as "bacteriophages" and pioneered the use of phages for treating Shigella dysentery in rural France. In 1917, bacteriophages were recognized as epizootic infections of bacteria (Summers, 2001). The first known report of successful phage therapy came from Bruynoghe and Maisin (1921), who used phages to treat staphylococcal skin infections (Johnson *et al*., 2008). Afterwards various workers documented that a tadpole like virus, bacteriophage is mainly responsible for bacterial killing hence can successfully be explored as a therapeutic agent against bacterial diseases (Tiwari and Hirpurkar, 2011; Tiwari *et al*., 2012). Bacteiophages can hypothetically be chosen to be harmless indirectly not only to the host organisms but also to other beneficial bacteria (like gut flora) as they are much more specific than antibiotics (Keen, 2012). The advent of molecular techniques like real-time polymerase chain reaction (RT-PCR); ribosomal RNA sequencing and laser-induced break down spectroscopy greatly facilitate the rapid selection of appropriate phages (Espy *et al*., 2006; Rhoads *et al*., 2012; Mohaidat *et al*., 2012).

Few salient features of phages:

- Bacteriophages are viruses which live on bacteria and have been proved to be best biocontrol agents by lysing the bacterial entities
- Unlike the antibiotics bacteriophages are viruses-living entities (in side host) that are the natural predators of bacteria
- Bacteriophages are consisted of genetic material (DNA or RNA) surrounded by a protein coat, a hollow protein tail and tail fibers. Bacteriophages are diverse group of viruses that subsit on bacteria and lead lytic or lysogenic life stages
- Bacteriophages can be detected by turbidity reduction method in the culture broth of a specific bacteria (Tiwari *et al*., 2012)
- They have been isolated by double agar overlay (DAL) method of Adams in the laboratory from different sources of waste water and sewages (Adams, 1950, 1959)
- Broiler chicks served as an in vivo biological filter to preferentially select bacteriophages capable of surviving in the adverse gastrointestinal environment. It clearly indicates that bacteriophages can be preferentially selected *in vivo* to increase survivability in the avian gastrointestinal tract (Yan and Polk, 2004)
- However, efficacy is required prior to use bacteriophage application for reducing species specific pathogenic infections such as *Shigella* and *Salmonella* infections
- In lytic condition, phages command the metabolic pathway of host bacterium for their own replication, multiplying there in and releasing kolin/lysin enzyme (Holin enzyme) to lyse host cell and allow released virion particles (about 20-200) to infect other bacterial cells (Matsuzaki *et al*., 2005)
- They are species specific, self-perpetuating, self-limiting and eco-friendly in nature (Parisien *et al*., 2008)

- The host specificity of phages for a particular type of bacterial agent, the ability of phages to replicate within infected animal hosts and the large margin of safety of phages make them efficacious antibacterial agents (Abedon and Thomas-Abedon, 2010)
- Frequent application of phage mixtures to improve the chances of success because of their property of killing a specific strain of the bacterium is noteworthy (Parfitt, 2005). Though being self-replicative entities inside the target host less doses are required

Applications of phages:

- **Replacers of antibiotics:** Bacteriophages are an attractive tool for antibacterial therapy (Shasha *et al*., 2004)
- **Food industry promoter:** For biocontrol of bacterial contamination of foodstuffs in the food industry (Rees and Dodd, 2006; Stone, 2002). Phages have been used in food-industry to reduce the load of Salmonella or Listeria over the fresh-cuts or poultry products (Leverentz *et al*., 2001; Leverentz *et al*., 2004)
- **Against plant diseases:** Protection of plants against bacterial infections (Balogh *et al*., 2010)
- **Guard of aquatic life:** For the control of water-borne pathogens and bacteria residing in water-bodies and aqua-cultures
- **Ubiquitous beneficial viruses:** In control of environmental microflora (Rakhuba *et al*., 2010)
- **Pre-slaughter treatment agent:** Phages can be used in animals preslaughter to minimize the bacterial load
- **Generally Recognized As Safe (GRAS) food additives:** Bacteriophage are approvd from the Food and Drug Administration (FDA) also for direct addition to food items for human consumption as they have the GRAS status
- **Effective remedial measure:** In crops and foods postharvest and in humans post-infection (Abedon, 2009)
- **Superbug therapy:** Well-controlled animal model studies demonstrated that phages can rescue animals from a variety of fatal infections and is very effective in treating drug-resistant infections of humans (Merril *et al*., 1996; Carlton, 1999)
- **Typing of bacteria:** Due to host specificity, phages are successfully being used in many microbiological labs in identification and confirmation of bacterial strains such as Gram positive *Staphylococcus*, *Listeria* and among Gram negative bacteria Salmonella species (Mehndiratta *et al*., 2010; Loessner and Busse, 1990)

Although, phage therapy has not gained that position in the market which it deserves and many hurdles are still to be overcome but it appears likely that sooner phage therapy will regain a role in both medical and veterinary treatment of infectious diseases, especially in the scenario of emerging antibacterial resistance (Duckworth and Gulig, 2002; Sulakvelidze and Morris, 2001; Sulakvelidze *et al*., 2001; Weber-Dabrowska *et al*., 2000).

Mode of action of bacteriophages: Bacteriophages are remarkably smart superbugs of bacteria as they are equipped with more than one/many strategies to kill their host. As bacteria are different types based on their cell wall structure protecting the cell protoplast from mechanical rupture and osmotic disbalance, bacteriophages also apply different pattern to convince the host bacterial cell for compromising its life. Phages can be lytic/virulent and lysogenic but in both the conditions they always have ability to control the cellular or replicative machinery of the host cell (Scientific Opinion of the Panel on Biological Hazards, 2009).

Phages kill the host by two ways:

- By lysis of host cell, owe to their lytic mode of replication
- By releasing Holins/endolysins/lysins- these are phage specific enzymes which can rupture the cell wall of bacteria and due to osmotic imbalance death of cell takes place

Cleverly, it is the decision of phage depending upon type of cell, Gram positive, Gram negative or acid-fast that which type of mode of replication should be adopted for its longer survival and better dissemination in the environment (Matsuda *et al*., 2005; Orito *et al*., 2004). It is however possible that many of the phages used in therapy act via a similar cascade as that of T4 phages but some of them may have some unique unidentified genes/ or mechanisms that enable them to effectively lyse their target bacteria. An anti-*Salmonella* phage gene responsible for the lethal activity of the phage against the *Salmonella enterica* serovar Typhimurium host strains is a classical example in this regard (Adamia *et al*., 1990).

Medical and veterinary science looking towards Phages: The pragmatic goal of phage therapy is to check the bacterial infection without initiating any side effect. Emerging strains of multi-drug resistant bacteria has encouraged the use of lytic phages in form of a proven therapy and has renewed the interest and enthusiasm to

use these phages as a potent candidate of antibacterial therapy (Levin and Bull, 1996; Skurnik and Strauch, 2006). Historical documentation of phage therapy of last 80-90 year against various bacterial pathogens such as *E. coli*, *Proteus*, *Salmonella*, *Shigella*, *Pseudomonas*, *Klebsiella*, *Mycoplasma*, *Acinetobacter*, *Listeria*, *Campylobacter*, *Vibrio*, *Streptococcus*, *Staphylococcus*, *Bacillus* etc are ever promising with the remarkable success-rate of 80-97% (Alisky *et al*., 1998, Barrow and Sothill, 1997; Gourlay, 1971; Carlton, 1999). Not only in animals but also in humans various conditions of burn infections, suppurative wound infections, lung infections involving pneumonia, gastro-enteritis, osteomyelitis and many nervine disorders of bacterial origin have also been treated by using cocktail of phages (Slopek *et al*., 1983; Dlopek *et al*., 1987; Tiwari, 2009; Tiwari *et al*., 2011).

Phages would have a high therapeutic index i,e., phage therapy would be expected to give rise to almost negligeable side effects and as phages replicate *in vivo* a smaller effective dose can preferably be used. Concentration of phages in the therapeutic preparations ranges from 10^{9}-10^{11} PFU/dose and can be used according to the kind of ailment either in topically by swabbing, spraying over the affected part or by injecting subcutaneously, intra-muscularly or intra-venously in animals, birds and humans (Pirisi, 2000; Tiwari *et al*., 2010; Tiwari *et al*., 2011).

Initially it was opined that phages can not infect the intracellular bacteria until it has entered inside the cell but later on studies revealed that few Mycobacteria are susceptible if they can be treated before their entry into the host cell with the specific mycobacterial viruses in the environment itself (Pedulla *et al*., 2003). Under such circumstances phages may play an active role against rapidly growing non-pathogenic mycobacteria, however certain lysogenic strains of Mycobacteria have also been detected (Buraczewska *et al*., 1971). On the other hand, it has been demonstrated that another intracellular bacteria *Brucella abortus* have effectively been subcided by the lytic phages even when added in the cell culture after being infected with the bacteria (Broxmeyer *et al*., 2002; Corbel and Morris, 1980; Hsia *et al*., 2000; Sakaguchi *et al*., 1989).

However, reports of success of phage therapy against the extracellular bacteria is abundant but against intracellular bacteria is scarce and only limited reports of *in vivo* studies are available elucidating the effects of phages against infections of Brucella, Chlamydia or Mycobacteria (Mankiewcz and Beland, 1964; Sulakvelidze *et al*., 2001; Shaw *et al*., 1983). Still, viruses against few intra-cellular bacteria are being documented (Zemskova and Dorozhkova, 1991). Bacteriophage against Mycobacteria has been referred as mycophage or mycobacteriophage by certain workers (Engel, 1978). Such phages have been isolated from a variety of sources viz; water, faeces (Cater and Redmond, 1963), soil (Froman *et al*., 1954), bacterial media (Sushida and Hirano, 1972) from healthy and diseased both type of individual (Emery and Whittington, 2004). Mycobacterial viruses such as PM/90/69, TM4, AG1 and ph60 have been found to be lytic against bovine, murine, BCG and *M. paratuberculosis* strain while V24 mycophage has shown sensitivity against rapidly growing mycobacteria only (Foley-Thomas *et al*., 1995; Cater and Redmond, 1960; Emery and Whittington, 2004; Tageldin *et al*.,1981). Till now there are no reports of mycobacteriophages against avian strains of tubercle bacteria. Phages effective against extracellular *Staphylococcus aureus* including methicillin resistant staphylococcal strains have also been detected and named as bacteiophage (M^{Sa}). Such phages can prevent formation of abscess along with reduction of bacterial load of abscesses and thus are proved to be effective against both local as well as systemic *S. aureus* infections (Qazi *et al*., 2004; Capparelli *et al*., 2007).

Cyanophages/Phycophages: Friend or Foe of algae: Besides, heterotrophic life forms, nature is rich in many phototrophic organisms including plants and various types of algae (Shilo, 1972). The first discovered virus Tobacco mosaic virus was virus affecting plants, further search of host range of viruses revealed that they can also infect the algae and cyanobacteria. Viruses infecting algae are called phycophages in general and when they infect blue green algae i.e., cyanobacteria, specifically they are referred as cyanophages (Martin and Benson, 1988; Padan and Shilo, 1973; Safferman and Morris, 1963; Sherman and Brown, 1974). These are double stranded DNA viruses harboring wide genetic as their genomic studies suggests that these are new viruses entering into genomic era (Suttle, 2005). Detailed studies have been done and valuable informations are available in the literature throwing the light on the wide distribution of phages in the nature, different water sources, lakes, sewage water etc., (Cannon *et al*., 1974; Hu *et al*., 1981; Shane, 1971; Shilo, 1972).

Blue green algae are considered and most sturdy type of weed of aquatic environment involved in the release of algal toxins, formation of blooms and scums in the fresh water rendering water unsuitable for the consumption purposes and for the life of surrounding marine fishes and mammals (Carmichael, 1981; Moore, 1981). As there is no completely effective herbicidal preparation is available against such weedy BGA species and still development of other alternative measures are in mid-way, cyanophages

may act as an effective means of controlling blooms produced by various genera of algae and cyanobacteria (Desjardins and Olson, 1983; Safferman and Morris, 1964a). *Lyngbya birgei, Anabaena flos-aquae, Microcystis aeruginosa, Anabaena circinalis, Phormidium, Nostoc*, marine brown algae *Feldmannia* and *Plectonema* are major bloom forming algae against which cynophage have been studied. LPP-1, LPP-2, Pheoviruses such as *Feldmannia irregularis* (FirrV-1) virus, cyanophage P-60 and Ma-LMM01 are main cyanophages, capable of infecting various members of Plectonema, Synechococcus, Feldmannia, Lyngbya and Phormidium genera (Chen and Lu, 2002; Delaroque *et al*., 2003). Algal viruses have been isolated by the method of chloroform extraction and used in the dose of 10^7 PFU/mL^{-1} (Franche, 1987; Safferman and Morris, 1964b). Production of plaques over the lawn of cyanobacteria is an indication of lytic activity of phycoviruses. Various studies performed in this area indicate the role of cyanophages, natural viruses of blue green algae in the biological regulation of population dynamics and control of blue green algae as a preliminary and an alternative effective approach (Phillips *et al*., 1990; Martin, 1982; Martin *et al*., 1978).

Mycophages: Threat to pathogenic fungi: Fungi are infectious agents producing mostly superficial infections, though systemic disease also prevails under immune compromised conditions in individuals or birds and animals. Due to long course of anti-fungal therapy, treatment of fungal diseases in large animals is considered as economically unjustifiable and in most of circumstances when animals are reared for meat purposes, it seems impractical as well. An interesting breakthrough in the scientific history came with the idea these fungal hyphae and yeast both, can also be infected by specific viruses (Lemke and Nash, 1974). Certain viruses may infect the fungus and have been isolated from various fungal species, such viruses are referred as fungal viruses or Mycophages and when they infect yeast are called as zymophages (Bozarth, 1972; Lindegren and Bang, 1961; Lindegren *et al*., 1962). There are more than hundred types of mycophages prevalent in the nature. Many viruses have been procured from fungi viz, Mycophage PS-$_1$ from *Penicillium stoloniferum* (Bozarth *et al*., 1971), mycophage of *Penicillium chrysogenum*, (Nash *et al*., 1973), mycophage from human pathogenic fungi *Blastomyces dermatitidis* (Kohno *et al*., 1994), from *Penicillium funiculosum,* virus against *Agaricus bisporus* mushroom (Dieleman-Van Zaayen, 1972; Dieleman-van Zaayen and Igesz, 1969) and mycophage from *Aspergillus foetidus* (Banks *et al*., 1970; Border *et al*.,1972; Borre *et al*., 1971). Initially, regarding mycophage concept was that they are not viruses but virus like particles based on interferon inducing property (Banks *et al*., 1968; Kleischmidt *et al*., 1968; Koltin *et al*., 1973). Virus like particles were isolated and identified in many fungal species such as *Penicillium brevi-compactum*, *Aspergillus flavus, Penicillium chrysogenum* by various workers at different places (Sansing *et al*., 1973; Wood and Bozarth, 1972; Wood *et al*., 1971; Wood *et al*., 1974). Those mycophages that enter into living fungal cells (endocellular biotrophs) are transmitted vertically. Many endocellular biotrophs live inside the mammalian cells viz. Burkholderia species (belonging to β-proteobacteria). *Candidatus Glomeribacter gigasporarum* which colonises the spores of *Gigaspora margarita* are entirely dependent on the metabolic functions of the fungal cells in which they live because of their shorter genome size. By performing centrifugation studies and based on electron microscopy it was made confirmed that these virus like particles contain ds RNA and are a mature virion, hence termed as mycophages (Leveau and Preston, 2008).

Isolation and purification of fungal viruses have successfully been tried (Van Frank *et al*., 1971). Based on EM studies and time calculated for thermal denaturation it was opinioned that other than Reo and Rice dwarf virus, mycophages also possess double stranded RNA as genome (Burnett *et al*., 1975; Wetmur *et al*., 1981). Mycophages are small, icosahedral, ds RNA viruses of 55 to 80 nm diameter size (Yamashita *et al*., 1973). These mycophages as a mature virion or as only ds RNA of mycophage alone, are capable of inducing interferons in cell cultures and in animals both. (Lampson *et al*., 1967; Planterose *et al*., 1970). Mycophages can be detected by serological studies with the help of specific antiserum against double stranded RNA (Moffitt and Lister, 1973). As they are specific for host fungi hence they can be modified and used in therapeutic preparations for the treatment of fungal diseases against many pathogenic fungi, therefore can be an alternative of anti-fungal therapy (Bozarth, 1972; Ghabrial, 1980).

Virophages: Parasites of viruses: Discovery of virophage is not only fascinating but also astonishing as the emergence of this new biological entity has started a debate regarding how much old viruses are? Virophages are virus infecting viruses which has give rise to a hypothesis whether viruses are oldest and first living form originated on the earth from which further higher forms evolved. Another theory/possibility is as they can also behave as non-living, whether they appeared as first form at the origin of earth waiting for origin of suitable host

under optimum conditions. Now, there is a track record that viruses can infect a wide range of hosts including viruses. In La Scola *et al.* (2008) in Paris discovered the first ever virophage and call it as 'Sputnik' virophage (La Scola *et al.*, 2008). Sputnik is a latin word, meant to satellite and phage (Greek; Phagein means-to eat) which means altogether a virus capable of eating another virus. In general term, virophages are considered as parasites of viruses. After the discovery of the very first virophage, till now, a total of 3 virophages have been identified. Virophages are double stranded DNA viruses of icosahedral symmetry infecting viruses present inside its host. Scientists were in doubt initially that sputnik is a small sized satellite virus or any independent newly evolving biological entity (Desnues and Raoult, 2012; Desnues *et al.*, 2012a; Fischer, 2011; Krupovic and Cvirkaite-Krupovic, 2011). Sequence analysis of sputnik phage showed that it shares genes of viruses capable of infecting various members of all three domains; Archaea, Bacteria and Eukarya (Desnues *et al.*, 2012b). However, emergence of virophages raises a question in front of biologists that why there should not be a fourth domain comprised of large DNA viruses, infecting viruses (Desnues *et al.*, 2012a). Host virus of sputnik is giant mimi virus, largest virus till date, which parasitizes a protozoan *Acanthamoeba polyphaga* (La Scola *et al.*, 2008; Sun *et al.*, 2010; Luther *et al.*, 2011; Zhang *et al.*, 2012). Mimivirus infects amoebae of the genus Acanthamoeba, member of the Mimiviridae family which includes nucleocytoplasmic large DNA viruses (Claverie and Abergel, 2009).

Virophages have exquisite specificity for their viral host, hence can extensively be used for genetic studies. Certain virophages take the credit of elucidating the evolution of eukaryotic genome by acting as evolutionary link between double stranded viruses (DNA/RNA) and mobile genetic element, designated as transposones (Desnues *et al.*, 2012b; Fischer and Suttle, 2011). Another virophage Mavirus infecting giant Cafeteria roenbergensis virus (CroV) of marine flagellate Cafeteria roenbergensis has been exploited to dig out the secrets of evolution of higher forms of life. Third virophage is ds-DNA, enveloped small sized virophage detected in the salty Organic lake of Antarctica and called as Organic Lake Virophage (OLV) found on algae already infected with a DNA phycovirus.

Applications of virophages: Biologists not only document the discovery of new biological agents but simultaneously explore all the possible dimensions of emerging pathogens. Similarly other than parasitizing on viruses, virophages also have multi-facet benefits, mentioned as below:

- As an anti-viral therapy: As now only three types of phages are known but it indicates that in the nature there can be presence of virophages against viruses infecting plants, animals, birds and human beings. Therefore, this area can be explored in detail to develop some alternative anti-viral therapy against large sized viruses (Koonin, 2012)
- Engineer of Ecological system: Virophage such as OLV, helps in maintaining the algal population in ocean because it prays over viruses affecting algae; plays role in diverse aquatic ecosystems by regulating host-virus interactions and in Organic lake influencing overall carbon flux. Microbial loop mediated secondary production is stimulated by virophages as they reduce overall mortality of the host and during polar summer light increase the frequency of blooms. In this way they contribute in the equilibrium of eco system (Madan *et al.*, 2005; Yau *et al.*, 2011)
- Role in search of seed of evolution: By comparing the sequences of jumping genes with those of double stranded DNA of virophages, evolutionary hierarchy is correlated thereby have influential impact in the study of genetic make-up of various species (Desnues *et al.*, 2012a)
- Live nature of viruses: Being infectious over other viruses, phages shows living nature of viruses in the nature (Van Etten *et al.*, 1991)
- Genetic recombination: As few phages contains genes which can be present in diversified members of three domains of living beings, hence virophages can successfully be used as an effective candidate for transfer of genes in between different species (Iyer *et al.*, 2006). In this regard, Sputnik virophages (those that are dependent on helper viruses for concurrent infection of the host cell) requires a special mention. They can act as vehicle to mediate lateral gene transfer between population of DNA viruses in the marine environment (Fischer and Suttle, 2011)

CONCLUSION AND FUTURE PERSPECTIVES

Bacteriophages are bacterial viruses that are ubiquitous in the environment. With increasing knowledge and modern technologies bacteriophages, virophages, mycophages, zymophages and cyanophages can exclusively be used for wide range of biological applications. There is no doubt in saying that their application in bio-control of pathogens will definitely

benefit the society as they are harmless to humans, hence can make a valuable contribution to food safety and public health. Although there are still many doors to be opened to know more about these double-edged biological entities and hurdles to overcome to employ them in therapeutic and prophylactic class of health science. Till now, available results are encouraging and there is an obvious need to develop phage therapy. Based on multi-dimensional characteristics, phages have proven to be valuable allies in mankind's fight against disease, have potential for control of both animals and zoonotic pathogens and show great promise as alternatives to effect loosing traditional antimicrobials. But major drawbacks associated with phage therapy are insufficiency and difficulty in funding as to patent bacteiophage products is a lengthy and complex process. Changes in regulatory stances of Food and Drug Administration (FDA) are therefore required to make phage therapy successful and more popular.

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