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Ganga River Bacteriophages: Navigating The Biotechnological Landscape For Future Applications

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Abstract- Bacteriophages isolated from river Ganga water are known as Ganga river bacteriophages. It has recently been discovered that Ganga river bacteriophages, which are naturally occurring predators of bacteria, can be effectively employed in contemporary biotechnology. For numerous bacterial strains that are resistant to antibiotics, they have been suggested as antibiotic substitutes. Phages from the Ganga river can be employed as biocontrol agents in the oil and agricultural sectors. Additionally, ganga river phages are employed as delivery systems for several proteins and antibodies, as well as for DNA and protein vaccines for the identification of harmful bacterial strains. Ganga River bacteriophages are a varied set of easily manipulable viruses that may have applications in research, biotechnology, and medicine. This review article's objective is to help the many academics, researchers, and biotechnologists who are utilising Ganga river phages in their practice, to accelerate the progress and development in the field of biotechnology.

1.0 Introduction

On Earth, bacteriophages are the most prevalent organisms. The genetic material of these bacterial viruses is encapsulated in a protein coat and can be either DNA or RNA [1]. The fiber-containing tail, to which the capsid is linked, is utilised to adhere to receptors on the surface of bacteria cells. Except for filamentous phages, the majority of phages contain polyhedral capsids [2]. Ganga river phages are causing bacterial infections that can spread through two different life cycles: lytic and lysogenic. The term "lytic life cycle" describes the phage life cycle, in which the phages destroy their hosts as they multiply vegetatively. However, some phages, referred to as temperate phages, are able to develop vegetatively and integrate their genome into the host chromosome, allowing them to replicate alongside the host for a number of generations [3]. The prophage will escape through bacterial lysis if it is exposed to severe circumstances, such as ultraviolet (UV) radiations [3]. Many researchers considered Ganga river bacteriophages' (phages') capacity to destroy bacteria, which might certainly make them viable medicinal agents, after their discovery in the early 20th century. However, this naturally occurring medicinal substance received little attention after World War II and

was only thought of as a research tool for many years [1]. This was before antibiotics were discovered. Ganga water bacteriophages continue to play an important role in the fields of molecular biology and biotechnology. Ganga water bacteriophages have solved a great deal of molecular biology's puzzles. Ganga water bacteriophages are gaining a lot of attention because of their prospective applications as antibacterials, phage display systems, and vaccine delivery vehicles in this highly advanced era [1]. They have additionally been employed for diagnostic (phage typing) purposes [1]. A summary of each of these applications may be found in this review article.

2.0 Phage therapy

The first application of phages as human medicinal agents occurred in 1919, the year of their discovery [4]. When Ernest Hankin initially revealed that there was antibacterial activity against Vibrio cholera, the cholera causative agent—then thought to be one of the worst threats to humankind—in 1896, phage therapy got underway [5]. Frederick Twort proposed in 1915 that the virus (phage) might be the cause of antibacterial action; however, Twort did not follow through on his findings, and Fe'lix d'He'relle discovered bacteriophages in 1917 [5]. Phage therapy gained interest when d'He'relle (1925) reported using antiplague phages to treat four different forms of plague. Later, he travelled to India and worked at the Haffkine Institute in Bombay (Mumbai) on phage therapy for the plague [6,65]. The development of antibiotics in the west caused the notion of phage therapy to become obsolete around 1940, but it was and is still in use in the former Soviet Union. When it comes to the broad research and application of phage therapy, the Eliava Institute in Tbilisi, Georgia, is regarded as a pioneer in this field [7].

Because of the early, inconsistent studies of phage therapy, West has remained hesitant to utilise it. Yet, phage therapy received attention in the United States. William Smith and associates documented the effective application of phages against Escherichia coli in mice [8].

The untrustworthy and uneven outcomes of several phage therapy experiments were among the factors contributing to the practice's avoidance in the majority of western countries. However, it is now acknowledged that inadequate knowledge of phage biology and a few other problems, such as insufficient quality control during the creation of therapeutic stocks, were the primary causes of the failure [9]. Humans, plants, and animals have all undergone phage therapy with varying degrees of effectiveness. In comparison to antibiotics, phages provide a number of potential benefits, but they also have drawbacks. The primary benefit of phages is their specificity for target bacteria, which significantly lessens the harm they cause to the host's natural flora. A combination of phages should be employed if the bacteria to be targeted cannot be identified beforehand. Because bacteriophages are self-limiting, they cannot survive long enough in the absence of the bacterial pathogens for which they are specialised [1]. Instead, they depend on their hosts' continuous growth. Phage replication occurs at the site of infection, which provides an additional benefit. They have few to no negative effects and are safe [10,11]. Another benefit of phages over antibiotics is that if bacteria develop resistance to them, phages will naturally evolve to infect the resistant bacteria, reducing the likelihood of bacterial escape [10]. Phages can spread rapidly throughout the body after administration, reaching practically every organ; nevertheless, the immune system quickly eliminates systemic phages, which presents additional obstacle to their acceptance as a therapeutic agent [12,13]. A robust antibody response that would clear the phages more quickly and prevent the use of phages for an extended period of time is one of the major concerns regarding the use of phage therapy in vivo [1]. Phage therapeutic drugs have limited host ranges and are not always lytic in specific physiological situations, which are additional downsides. To prevent secondary infections, it is imperative to guarantee that phage preparations are devoid of bacteria and bacterial toxins

during the phage stock manufacturing process. Phage sterilisation, however, may render them inactive. Phages can provide bacteria harmful characteristics that increase their pathogenicity [5]. Using the phage lytic enzyme endolysin as an alternative to ingesting the entire virion is one method [14-16]. In a similar vein, phages that have undergone genetic modification can be employed; these phages will only transfer the DNA required to produce antibacterials that are unique to the intended target bacteria [17]. Phage therapy may not be able to completely replace antibiotics in the near future, but it is hoped that it will be used in addition to them, particularly for types of bacteria that are resistant to antibiotics [1]. When phages are applied externally and given a chance by the immune system to stay in the body for a short while, they will be far more dependable [1]

3.0 Phage display

In 1985, the idea of phage display was originally presented [18] (Figure 1). A molecular method called phage display is employed to create polypeptides with unique properties. The desired protein is expressed on the surface of the phage particle when the DNA encoding the polypeptide is fused with the genes encoding the phage coat protein [18, 19]. Although the E. Coli filamentous phage M13 is widely utilised for phage display, other phages such as lambda and T7 are also employed in the phage display system [20, 21]. Phage display libraries are a useful tool for highly selective peptide screening and separation based on their affinity for target proteins. These peptides reduce receptor mimics and can be utilised as reagents in drug design to learn about molecular recognition [19]. These peptides can function as agonists or as inhibitors of receptor-ligand interaction to be exploited as therapeutic medicines. Furthermore, infections and other substances deemed to pose a risk to the environment can be found using these proteins [22]. It is possible to improve the enzymatic activity and binding characteristics of proteins through directed evolution [23]. The enzyme's activity is raised and its active site is haphazardly changed [1]. Utilising phages to display the Fab antibody fragments library mostly on filamentous phage surfaces allows for additional variation in phage display [24]. These libraries are used in numerous scientific applications, but one of the most significant ones is in the treatment of cocaine addiction. Phages are delivered nasally and eventually enter the central nervous system (CNS). The shown antibody attaches to the cocaine molecule in the central nervous system and prevents it from acting on the brain [25]. Phage display is now a fantastic aspect of biotechnology because to extensive and cutting-edge study conducted by numerous scientists. Phage antibodies have transformed the idea of therapeutic medications and drug design, among other uses [19]. Phage display provides a clear explanation for both protein-ligand interaction and molecular evolution [21].

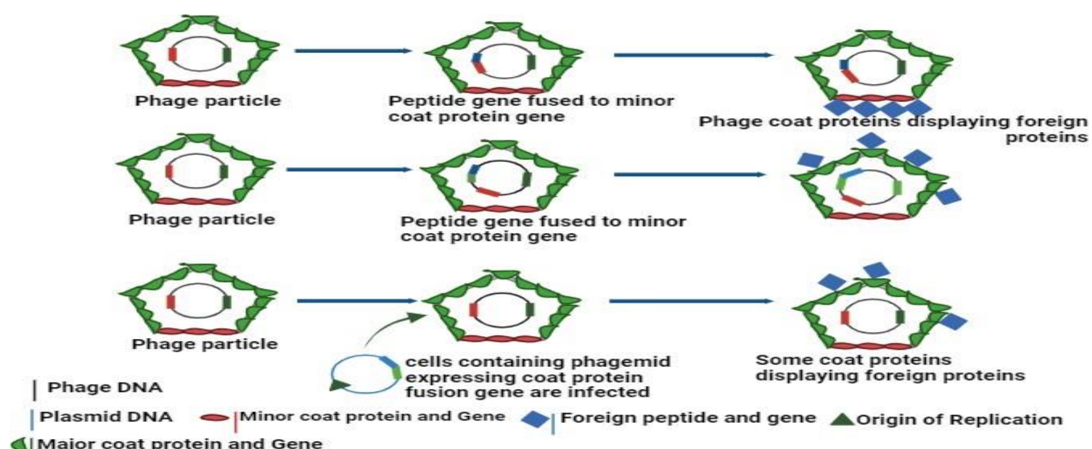

Fig.2 Several techniques for fusing foreign peptides onto the phage surface. Multiple phage coat proteins have the ability to show foreign peptides. More of the smaller foreign peptides are visible, however, this also depends on the phage, coat protein, and type of antigen. (a) The minor coat-protein gene is directly fused to the gene encoding a foreign peptide. All minor coat proteins exhibit the foreign antigen. (b) The major coat protein gene has a foreign peptide gene connected to it, and the major coat protein gene is present in duplicate. Some of the main coat proteins have foreign proteins on them. (c) Unaltered helper phages are introduced into cells harboring phagemids (plasmids with bacteriophage and plasmid origins of replication), which subsequently express the foreign peptide or protein. Certain coat proteins exhibit foreign antigens.

4.0 Phage typing

Phages can be utilised for pathogenic bacterial detection and strain characterization because of their sensitivity for bacterial cells [1]. The process of accurately identifying microbial strains through the use of sensitivity patterns to certain phages is called phage typing. If particular antibodies are able to identify the phages attached to the bacteria, the sensitivity of the detection will be raised [26]. Different phages are used to detect unknown bacterial strains on their lawn; if the plaque (clear zones) forms, the phage has grown and destroyed the bacterial cell, making the strain identification process straightforward [1]. Other techniques, such as the use of phages that specifically convey reporter genes {e.g. lux}, can be utilised to identify harmful bacteria [27] or by employing green fluorescent protein, which [28] would express during bacterial infection. In a similar vein, selective adsorption can be detected by phages that have a fluorescent dye covalently linked to their coats [29, 30] the identification of certain components that were released, namely adenylate kinase [31] after the targeted lysis of bacteria, phage-displayed antibodies and peptides that bind selectively to toxins and bacterial pathogens can also be employed [22]. Another way to employ phages to identify bacteria is using dual phage technology, which uses phages to identify when an antibody binds to a certain antigen [7]. Pathogenic microorganisms can also be found using the phage amplification assay [32]. The most common uses of the approach are for the identification of Salmonella, E. Coli, Mycobacterium tuberculosis, Listeria, and Campylobacter species [33].

5.0 Targeted gene delivery through Phages

Potential therapeutic gene delivery vehicles are phages [33, 34]. The idea behind utilising phages for targeted gene delivery is comparable to the idea behind using them to administer DNA vaccinations, since the phage coat shields the injected DNA from deterioration. However, logically speaking, they differ. Successful gene therapy requires that phages be able to target certain cell types, which is made possible by their capacity to show foreign proteins on their surfaces [1]. Targeting and processing compounds are displayed on phage surfaces by phage display and artificial covalent conjugation [35, 36]. Targeting sequences, such as fibroblast growth factor, have been employed to deliver phages to cells with the necessary receptors [37, 38]. Protein sequences like the penton base of an adenovirus, which mediates entry, attachment, and endosomal release, are employed to enhance phage absorption and endosomal release [39]. To improve the absorption and nuclear targeting of phages such as lambda that have been modified, the protein transduction domain of human immunodeficiency virus (HIV) tat protein and the simian virus 40 (SV40) T antigen nuclear localization signal have also been employed [40]. Moreover, integrin binding peptides that improve binding and uptake [37] and DNA degradation peptides that decrease DNase II inhibitor [38] have been shown to aid in gene transfer using phages. Phage display libraries have been utilised in mice repeatedly to screen phages for their capacity to target particular cells and tissues; each time, phages

were discovered in the targeted tissues [41]. For example, to isolate liver-targeting phages, mice were injected with phage display libraries, and the phages were separated from the livers [1]. The isolation of phage-displayed peptides that improved cytoplasmic absorption into mammalian cells is accomplished using a similar in vitro method [42]. Once more demonstrating their versatility, phages allowed for the targeting of particular tissues through either random or purposeful construction of phage display libraries [1].

6.0 Phages as vehicles for vaccines delivery

Phages have been employed as vaccine delivery systems (Figure 2). Phage particles with the vaccination antigens expressed on their surfaces can be utilised directly. However, in the case of DNA vaccines, the phage genome incorporates the sequences necessary for the manufacture of the vaccine antigen, and the phage serves as a delivery system for the DNA vaccine [13]. It is possible to create phages that would exhibit the particular antigenic peptide on their surfaces by using phage display [1]. A particular antiserum can be used to screen phage display libraries in order to find new antigens and mimetopes. Mimetopes are peptides with distinct primary structures that imitate the secondary structures and antigenic characteristics of protective proteins, lipids, or carbohydrates [43, 44]. In order to find possible vaccines against particular diseases, phage display libraries can also be screened against convalescents' serum [45]. Whole phage particles displaying antigenic peptides have occasionally been utilised as vaccinations in animal models [46, 47]. The spectrum of antigens shown can be expanded by intentionally conjugating some molecules to the phage surface after development, as opposed to transcriptional fusion to a coat protein [48]. Since phage coat proteins are thought to be natural immunostimulators [13,49], an antigen delivered on them would arrive "ready conjugated" with an inherent adjuvant activity, negating the requirement for further protein purification and conjugation to a carrier protein prior to immunisation. It has recently been demonstrated that DNA vaccines can be delivered more effectively using unaltered phages than through conventional plasmid DNA vaccination [13,50,52].

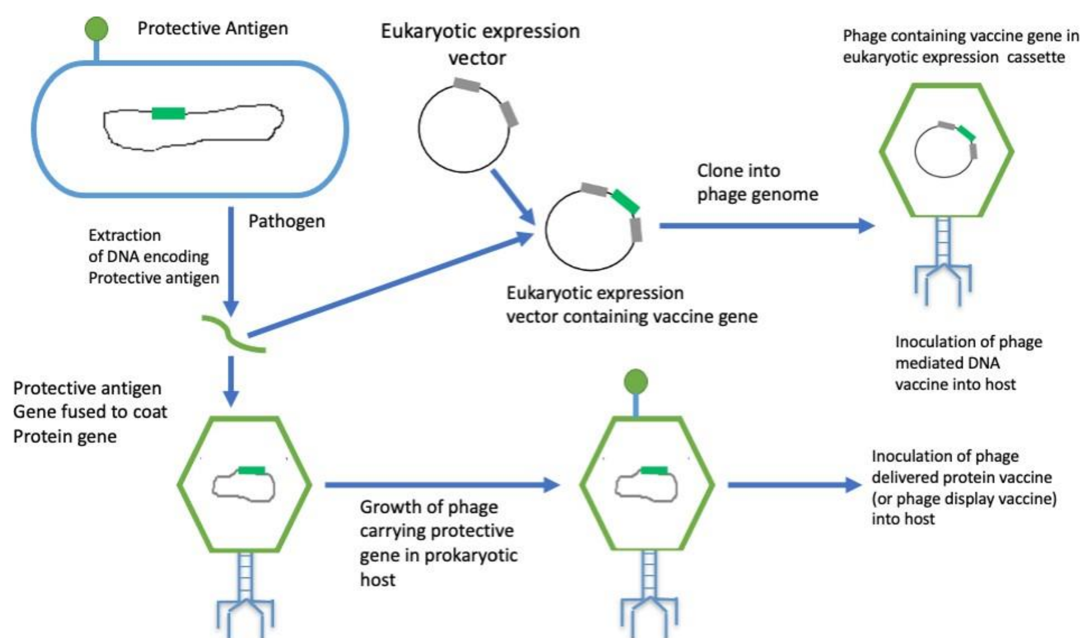

Fig.2 Diagrammatic representation of two vaccine delivery methods using phages: phage DNA vaccine and phage display vaccine.

The vaccine gene is cloned in a lambda bacteriophage using a eukaryotic expression cassette, and the purified phage particles are then injected into the host. The coat shields DNA from deterioration and directs the vaccination towards antigen-presenting cells by functioning as a virus-like particle [1]. In mice [52] and rabbits [50], the antibody response was significantly higher compared to the usual DNA immunisation. It has recently been suggested that a hybrid phage might be created, with a phage display variant of the same antigen displayed on the phage surface and a DNA vaccine enclosed in the phage particle under the eukaryotic promoter [1]. A vaccination of this kind would effectively target the cellular and humoral immune systems [13]. It can also be used to modify the phage vaccine's surface by adding particular protein sequences that target different types of immune cells, such as galactose residues that target the liver's hepatic receptors that recognise galactose [48]. Similarly, peptides isolated from phage display libraries [54] could be used to target langerhans cells and dendritic [53].

7.0 Phages as biocontrol and bacteriophage bioprocessing

Phages are potentially useful as predators of pests (bacteria) that are associated with plants, fungus, or the products that they produce [55, 56]. To treat infections of peaches, cabbage, and peppers, phage-mediated biocontrol of plant pathogens has been successfully applied to the bacterial spot of peaches linked with Xanthomonas pruneni. Phages have also been employed in the management of tobacco's Ralstonia solanacearum. They have been effectively used to combat tomato spot-causing Xanthomonas campestris. Phage treatment is also an option for Pseudomonas tolaasii-induced bacterial blotches on mushrooms [57]. Phages have also been taken into consideration as a way to manage the biofouling of condenser tubes in thermal power plants [58]. Using bacteriophages in bioprocessing reduces the number of bacteria in food, usually in minimally processed foods to prevent cooking-related flavor or texture [59]. Since fruits and vegetables cannot be further processed to eliminate any pathogens, controlling pathogens with phages is a non-thermal intervention that reduces the growth of Salmonella and Campylobacter on chicken skin [60], Salmonella enteritidis in cheese [61], Listeria monocytogenes on meat [62], and fresh cut fruit [63,64]. Phage bioprocessing could be used to extend the shelf life of animal products [64,66].

8.0 Conclusion

The information above provides a taste of the many uses for phages in the fields of biotechnology and medicine. Phage typing is one method of diagnosing diseases; phage vaccines are used to prevent them; and phage therapy is used to treat them. It is hoped that phages will be beneficial to humans in several ways. A wide range of bacterial illnesses that would ordinarily be resistant to the most recent generations of antibiotics could be easily treated by creating a cock tail of phages. Because phages have the ability to lyse bacteria, they can be utilised separately to treat bacterial infections. The adaptability of phages would also enable us to use antibodies against the bacteria that have been exposed to the surface of the phage. A DNA vaccine or phage display vaccination could also be used to deliver a protective antigen. Therefore, a variety of genetically altered phages would be more beneficial in solving all of these issues. Phages have proven to be effective in treating bacterial infections in plants and fruits as well as in managing the issue of food spoiling. The usage of phages raises some questions. It covers the questions of safety and effectiveness as well as the body's reaction to the phages that were given. Phage growth optimisation and purification techniques are other difficulties that must be addressed. It is thought that these organisms, known as phages, which are widely distributed across the biosphere, could provide answers to a variety of

concerns that people have due to the quick advancements in the fields of molecular biology and biotechnology.

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