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POTENTIAL UTILIZATION OF ANTIPLASMID AGENTS WITH BIOENGINEERED BACTERIOPHAGE DELIVERY MEDIA AS THE LATEST STRATEGY TO TREAT ANTIBIOTIC RESISTANCE

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ABSTRACT

Infectious disease can be interpreted as a disease caused by infectious agents (bacteria, viruses, fungi, and parasites) or toxic products that are transmitted from infected people, animals, and reservoirs, either directly or indirectly. The main therapy for infectious diseases, especially bacterial infections, is to use antibiotics. However, the massive use of antibiotics and the tendency to frequently abuse them have led to the development of antibiotic resistance in pathogenic bacteria. Therefore, a new solution is needed to overcome the high rate of antibiotic resistance. Bacteria can develop resistance characteristics through two main mechanisms. The first mechanism is by carrying out intrinsic genetic mutations that support the achievement of resistance traits, while the second mechanism is by the acquisition of mobile genetic elements. Plasmid-mediated resistance is one of the important mechanisms in increasing antibiotic resistance. Antiplasmid agents are compounds that are capable of inhibiting plasmid replication, which in turn results in the elimination of bacterial plasmids. Various compounds have the potential to be used as antiplasmid agents, for instance, DNA intercalating agents, psychotropic drugs, detergents, biocides, and various compounds derived from herbs. One of the biggest challenges of antiplasmid therapy is the fact that most antiplasmid agents are mutagenic, carcinogenic, and teratogenic when they attack human cells. Therefore, the use of engineered bacteriophage has the potential to be used as a delivery medium for antiplasmid agents to go directly to pathogenic bacteria without damaging the body cells.

1. Introduction

Infectious disease can be interpreted as a disease caused by infectious agents (bacteria, viruses, fungi, and parasites) or toxic products that are transmitted from infected people, animals, and reservoirs, either directly

or indirectly [1]. Infectious disease remains a major issue in the world, especially in developing countries and low-income countries. Data gained from the World Health Organization (WHO) shows that in 2016, three of the ten most common causes of death in the world were caused by infectious diseases [2].

The main therapy for infectious diseases, especially bacterial infections, is to use antibiotics. However, the massive use of antibiotics and the tendency to frequently abuse them have led to the development of antibiotic resistance in pathogenic bacteria. Data reveals that more than half of hospital patients received antibiotics and 40% of them used antibiotics not according to the indications [3]. Research estimates that antibiotic resistance will cause the death of ten million people per year globally by 2050 [4]. In line with this finding, data on bacterial sensitivity patterns in several hospitals in Southeast Asia show similar results. The number of antibiotic-resistant bacteria such as *methicillin-resistant Staphylococcus aureus* (MRSA) is 13-26%, *extended spectrum β-lactamase* (ESBL) in *Escherichia coli* is 25-57%, and ESBL in *Klebsiella pneumoniae* is 32-56% [5].

Due to the aforementioned facts, various efforts have been made to overcome antibiotic resistance such as efforts to discover new antibiotics as well as programs to control and supervise antibiotics. However, since 2000, new antibiotics have been difficult to develop and in the last 14 years, development has been limited to modifications of existing antibiotics [6]. Therefore, a new solution is needed to overcome the high rate of antibiotic resistance. The potential utilization of bacteria antiplasmid agents with bioengineered bacteriophage delivery media is seen as the latest innovation in treating antibiotic resistance.

2.1 The Role of Plasmids in the Development of Antibiotic Resistance

Bacteria can develop resistance characteristics through two main mechanisms. The first mechanism is by carrying out intrinsic genetic mutations that support the achievement of resistance traits, while the second mechanism is by the acquisition of mobile genetic elements such as plasmids, transposons, and integrons through horizontal gene transfer [7]. Plasmid-mediated resistance is one of the important mechanisms in increasing antibiotic resistance and is defined as the presence of an antibiotic resistance gene encoded by a bacterial plasmid [8].

In general, plasmids are located separately from the main bacterial chromosome and have the ability to replicate independently. Most plasmids contain the genes needed to help bacteria survive in unfavorable environments, including to survive and thrive even though there are antibiotics that have the potential to kill bacteria. Therefore, plasmids have a major role in creating antibiotic resistance. Moreover, plasmids also contain genes that can synthesize additional enzymes that can destroy toxic substances to bacteria [9].

Plasmid-encoded and mediated antibiotic resistance encompasses most, if not, all classes of antibiotics currently used in the clinics. Bacteria have developed resistance to various important antibiotics such as cephalosporins, fluoroquinolones, and aminoglycosides [10]. Plasmids that have antimicrobial resistance genes are often found, especially in gram-negative bacteria. These genes include genes encoding ESBLs such as *CTX-M*, genes encoding carbapenemases such as *NDM-1*, *KPC*, and *OXA-48*, and colistin resistance genes such as *MCR-1* [11].

Currently, *NDM-1* has been found in various countries and is reported to cause many serious nosocomial infections [12]. In addition, *KPC* has also been reported to cause many nosocomial infections, especially in the United States, China, Israel, and Greece [13]. The *KPC* group is able to hydrolyze all β-lactam antibiotic agents, including monobactams and carbapenems. Furthermore, carbapenemase *OXA-48* has also been reported to have an increased incidence, especially in cases of nosocomial infection [14].

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In addition to the aforementioned genes, other genes were also discovered on plasmids that coded for resistance to quinolone-class antibiotics. The first gene found in a plasmid that was capable of causing resistance to quinolones was named *qnrA*. Since its first discovery, four other genes have been revealed that have a similar effect to the first gene, namely *qnrS, qnrB, qnrC,* and *qnrD* [15]. These genes can cause resistance because they encode proteins that are able to protect bacterial DNA gyrase which becomes the target of quinolone-class antibiotics [16].

Other studies have also demonstrated the existence of an antibiotic resistance mechanism by using bacterial membrane efflux pump procedures encoded by genes on bacterial plasmids, such as the *oqxA, oqxB*, and *tetA* genes [17]. The presence of efflux pumps in bacterial membranes allows microorganisms to regulate the internal environment of bacteria by eliminating toxic substances, antimicrobial agents, and other metabolites that have the potential to endanger bacterial life by pumping these compounds out of the bacterial cell thereby inducing antibiotic resistance [18].

2.2 Potential Utilization of Antiplasmid Agents in Handling Antibiotic Resistance

Antiplasmid agents are compounds that are capable of inhibiting plasmid replication, which in turn results in the elimination of bacterial plasmids [19]. Various compounds have the potential to be used as antiplasmid agents, for instance, DNA intercalating agents, psychotropic drugs, detergents, biocides, and various compounds derived from herbs [20], [21]. Antiplasmid agents can also work with a variety of mechanisms. One of the work mechanisms of antiplasmid agents is their ability to insert plasmid DNA, causing disruption of plasmid replication as DNA intercalating agents and chlorpromazine does. Other mechanisms include DNA severance as performed by the ascorbic acid antiplasmid agent and mediation of plasmid supercoiling as practiced by aminocoumarins [20].

Examples of DNA intercalating agents that can potentially be used to eliminate plasmids containing antibiotic resistance genes are acridine orange, ethidium bromide, and acriflavine. Acridine orange has been shown to have a plasmid elimination effect and is able to reduce the level of resistance of *Escherichia coli, Vibrio parahaemolyticus*, and *Lactobacillus sp* to antibiotics [22]. Ethidium bromide has also been shown to be able to eliminate plasmids containing the ^{bla}KPC-3 and ^{bla}TEM-1 genes in *Enterobacter aerogenes* as well as to be able to eliminate the plasmids of *Bacillus cereus* [23].

Intercalating agents are agents capable of inserting into plasmid DNA causing deformation and uncoiling of plasmid DNA. The deformation that occurs inhibits the plasmid DNA from being able to replicate and function normally [24]. The continuous process of DNA intercalation can lead to the relaxation and elimination of plasmid DNA. The intercalation of various compounds into plasmid DNA can be proven by an increase in the melting point of the DNA and the presence of circular dischroism. Various studies have also been conducted to reveal the ability of intercalating agents to open and damage the plasmid circular structures [25]. Apart from the intercalating agents, psychotropic drugs are currently being widely studied because not only do they have anticommensal activity against bacteria, but psychotropic drugs also have the potential to be used as antiplasmid agents. One of the potentially used psychotropic drugs is a phenothiazine. This drug has been shown to be able to eliminate plasmids containing antibiotic resistance genes [26]. Research has shown that chlorpromazine, a drug from the phenothiazine class, is able to eliminate the *qacA* gene in bacterial plasmids which functions in encoding bacterial membrane efflux pumps. In addition to chlorpromazine, other drugs from the phenothiazine class such as thioridazine and promazine also have the potential to be used as antiplasmid agents because of their similar structure and effect, which causes the elimination of bacterial plasmid [27].

The working mechanism of psychotropic drugs as antiplasmid agents is not known for certain, however, research indicates that there is a link between the molecular structure of compounds in psychotropic drugs with their ability to change and cause bacterial plasmid deformation. Research reveals that antidepressants that have a planar tricyclic structure with side chains in the form of secondary amines are more effective in eliminating bacterial plasmids compared to antidepressants with side chains in the form of tertiary amines. Antidepressants with quaternary amine side chains are very weak in modifying and eliminating plasmids, presumably because these groups fail to penetrate the bacterial cell membrane [28].

Apart from DNA intercalating agents and psychotropic drugs, detergents such as bile salts and *sodium dodecyl sulfate* (SDS) are also potentially used as antiplasmid agents. SDS compound is an anionic detergent that is proven to have the ability to eliminate plasmids with genes that induce antibiotic resistance in *Pseudomonas aeruginosa*. Other studies have demonstrated the effectiveness of SDS in eliminating bacterial plasmids *Lactobacillus sp.*, *E. coli,* and *K. pneumoniae* [29]. Bacteria containing plasmids are suspected to be more sensitive to SDS due to the presence of plasmid-specified pili on their cell surface. SDS chemicals work as strong ionic detergents that can denature plasmid DNA, thereby, they inhibit the work of plasmids and their genes to develop antibiotic resistance [30].

In addition to the various compounds mentioned above, antiplasmid potential can also be found in various plant derivatives, such as in the extracts of *Plumbago zeylanica, Terminalia chebula, Alpinia galanga,* and *Dioscorea bulbifera*. Antiplasmid properties in various plant derivatives are superior for use in humans because they are non-toxic and do not cause mutagenic, carcinogenic, as well as teratogenic effects on human body cells [19].

Currently, *Plumbago zeylanica*, or what is commonly known as “godong encok” in Java has been extensively studied and has the potential to be used as an antiplasmid agent. “Godong encok” are shrubs that are similar to perish roots and have a height of 1-2.5 m and usually live on the outskirts of forests, fields, or yards as living fences [31]. The roots of this “daun encok” plant can be used because they contain the lawsone compound which is evident to have properties as an antiplasmid agent [19].

Research using DNA gel electrophoresis analysis showed that the bacterial plasmid band once existed before the extract of “godong encok” was given. Nevertheless, it was no longer detectable once the extract was given, demonstrating its potential as an antiplasmid agent. The mechanism of lawsone in “daun encok” plants acts as an antiplasmid by inhibiting bacterial plasmid replication and inter-bacterial plasmid transfer through conjugation [19].

In addition to “daun encok” plants, another plant that has the potential to be used as an antiplasmid agent is *Terminalia chebula* or commonly called the haritaki plant. This plant is mostly found in India and spread to Southeast Asia. Studies revealed that this plant’s extract was able to eliminate antibiotic-resistant plasmids such as pARI-815 and pUB-110 in *Shigella sonnei* and *Bacillus subtilis* [32].

2.3 Potential Utilization of Bacteriophage in the Antiplasmid System

Bacteriophage is a virus that is capable of infecting and replicating in bacterial cells. Bacteriophage is the most abundant organism on earth and has a crucial role in microbial physiology, microbial population control, and microbial evolution as well. There are various work mechanisms of bacteriophage, one of which is conventional bacteriophage or commonly called lytic bacteriophage [33].

Infection of lytic bacteriophage begins with the adsorption of bacteriophage at specific receptors located on

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the surface of the bacteria. These receptors can be located on the cell wall of gram-positive and gram-negative bacteria, the bacterial polysaccharide capsule, or on the bacterial pili [34]. It is this relationship between the bacteriophage and its receptor that will determine the spectrum of bacteria that can be infected by the bacteriophage. After the bacteriophage binds to specific receptors on the surface of the bacterial cell, the bacteriophage injects genetic material and other additional materials into the bacterial cell. After that, the virus will take over the bacterial replication to form another bacteriophage progeny and lyse the bacterial cell [35].

One of the biggest challenges of antiplasmid therapy is the fact that most antiplasmid agents are mutagenic, carcinogenic, and teratogenic when they attack human cells. Therefore, the use of engineered bacteriophage has the potential to be used as a delivery medium for antiplasmid agents to go directly to pathogenic bacteria without damaging the body cells. This engineered bacteriophage is then referred to as bioengineered bacteriophage [36], [37].

In the bioengineered bacteriophage method, antiplasmid agents that are toxic and carcinogenic can be attached to the coat protein p8 molecule found on the surface of the filamentous bacteriophage. This modified bacteriophage is then targeted to bind to pathogenic bacteria so that the antiplasmid agents can be delivered directly to the bacterial cells without inducing damage to the body cells [37].

In molecular biology, the coat protein is a protein with an alpha-helix structure that forms part of the filamentous bacteriophage envelope. Meanwhile, a filamentous bacteriophage is a rod-shaped bacteriophage about one to two micrometers long and six nanometers in diameter with a helical shell of protein subunits surrounding the DNA core. In the figure shown below, the filamentous bacteriophage has an envelope composed of the coat protein p8. It is this p8 coat protein that can be conjugated with neomycin via the terminal N-carboxyl side chain. Each neomycin molecule can then be conjugated with an antiplasmid agent through a labile ester bond linker. Ultimately, this design of the bacteriophage allows the antiplasmid agents to be delivered directly to the bacterium [38].

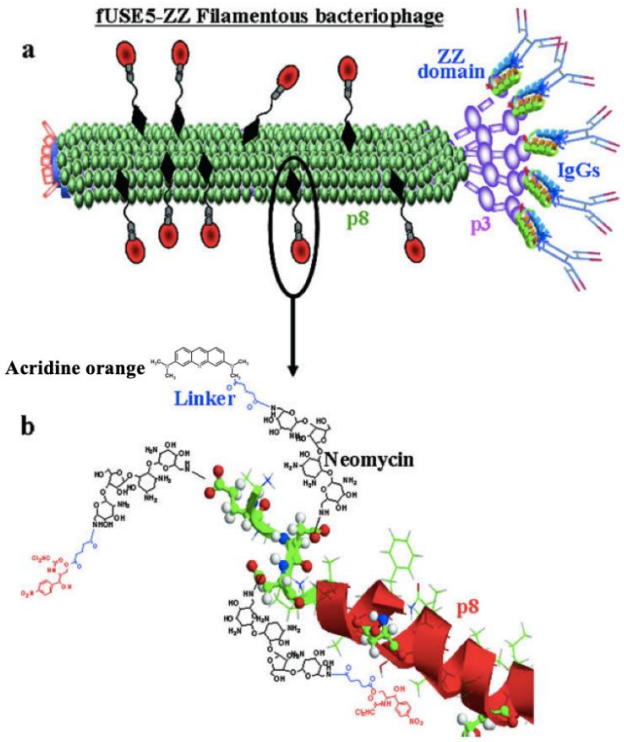

Figure 1. The attachment mechanism of the acridine orange antiplasmid agent to the coat protein p8 molecule on the surface of the bacteriophage [38]

Another technique that can be used to modify bacteriophage is phage display technology. Currently, various phage display technologies are being examined, including their potential as drug delivery media and chemical compounds [39]. In this technique, the nucleic acid of the bacteriophage is modified to induce the expression of certain proteins. This new protein can bind to specific parts of the target bacterial cell. The main implication of phage display technology for its use as a delivery medium for antiplasmid agents is that bacteriophage can be modified so that it has cell-penetrating peptide (CPP) which can help the penetration of antiplasmid agents into bacteria [40].

This CPP finding is actually one of the latest discoveries that allow antiplasmid agents not only to be delivered to the surface of bacterial cells but also to penetrate into bacteria and allow the antiplasmid agents to attack plasmids directly. CPP peptides work by binding to the receptors that induce endocytosis on the surface of the bacterial cells. Until now, CPPs that have been identified and have the potential as antiplasmid delivery media are HN-1, pep-7, 439a, and 439b [41].

In addition to attaching antiplasmid agents to bacteriophage, bioengineered bacteriophage can be used to deliver antibiotics and photosensitizing agents directly to bacteria. One of the studies on bioengineered bacteriophage has succeeded in attaching chloramphenicol to lytic bacteriophage so that antibiotics can be delivered directly to the bacteria. The results of this study reveal that the use of bioengineered bacteriophage can increase the potency of antibiotics by 20,000 times and reduce the side effects of drugs on healthy body cells because they work directly on intracellular bacteria [37].

Another potential utilization of bacteriophage in the antiplasmid system is the presence of bacteriophage that specifically has targets in the form of plasmids containing antibiotic-resistance genes, one of which is bacteriophage PRD1. The PRD1 bacteriophage was shown to be able to reduce the number of resistant plasmids from 100% to 5% after ten days of therapy on *Escherichia coli* and *Salmonella sp.* which is antibiotic resistant [42]. In addition, PRD1 is also able to reduce the K12 RP4 transconjugant of *E. coli* [43].

Another advantage of using bacteriophage in the antiplasmid system is its specificity. Direct bacteriophage therapy is aimed at attacking pathogenic bacteria, in contrast to antibiotics which have the potential to cause additional damage by disturbing the normal microbiota. The consequence of this specificity is that bacteriophage therapy is harmless to body cells and can ensure that the normal microbiota remains intact during therapy. The specificity of the bacteriophage also helps prevent secondary infections due to disruption of the normal microbiota such as oral candidiasis, pseudomembranous colitis caused by *Clostridium difficile*, and antibiotic-associated diarrhea [44].

3. Conclusion

Antibiotic resistance is a serious issue because it reduces the effectiveness of treatment, increases the transmission rate of infection, and costs a lot of money for treatment. Antibiotic modification and antibiotic monitoring and control programs are not optimal in dealing with the increasing number of antibiotic resistance. Based on this, it is necessary to develop a breakthrough therapy that is more effective in reducing mortality and morbidity due to antibiotic resistance.

Plasmid-mediated resistance is one of the important mechanisms for the development of antibiotic

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resistance. Therefore, antiplasmid agents have the potential to be used as a therapy to control antibiotic resistance. Antiplasmid agents such as DNA intercalating agents, psychotropic drugs, detergents, biocides, and various herbal-derived compounds can inhibit and eliminate bacterial plasmids that can induce resistance. However, the weaknesses of these antiplasmid agents are the fact that they are mutagenic, carcinogenic, and teratogenic in human body cells when administered directly. Therefore, antiplasmid agents are combined with bioengineered bacteriophage as a delivery medium so that antiplasmid agents can work directly on bacteria without damaging human body cells.

Accordingly, further research is needed, both in vitro tests and clinical trials regarding the potential of antiplasmid compounds with bioengineered bacteriophage delivery media as a therapy in treating antibiotic resistance. Furthermore, it is hoped that this therapy can be applied clinically and can be used by the community to control as well as reduce antibiotic resistance both in Indonesia and in the world.

4. References

[1] Lindahl JF, Grace D, Lindahl JF, Grace D. The consequences of human actions on risks for infectious diseases: a review. 2017;8686(May).

[2] World Health Organization. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region. Geneva; 2018.

[3] Utami ER. Antibiotika, resistensi, dan rasionalitas terapi. 2012;124–38.

[4] O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report And Recommendations The Review On Antimicrobial Resistance. 2016;(May).

[5] Kakkar M, Chatterjee P, Chauhan AS, Grace D, Lindahl J, Beeche A, et al. Antimicrobial resistance in South East Asia: time to ask the right questions. Glob Health Action [Internet]. 2018;11(1):1483637. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29921172

[6] Renwick MJ, Brogan DM, Mossialos E. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. J Antibiot (Tokyo). 2016 Feb;69(2):73–88.

[7] van Hoek A, Mevius D, Guerra B, Mullany P, Roberts AP, Aarts H. Acquired antibiotic resistance genes: an overview. Front Microbiol [Internet]. 2011 Sep 28;2:203. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22046172

[8] Shintani M, Sanchez ZK, Kimbara K. Genomics of microbial plasmids: classification and identification based on replication and transfer systems and host taxonomy. Front Microbiol [Internet]. 2015 Mar 31;6:242. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25873913

[9] Tsang J. Bacterial plasmid addiction systems and their implications for antibiotic drug development. Postdoc J a J Postdr Res Postdr Aff [Internet]. 2017 May;5(5):3–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28781980

[10] Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr [Internet]. 2016 Apr;4(2):10.1128/microbiolspec. VMBF-0016–2015. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27227291

[11] Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis. 2016 Feb;16(2):161–8.

[12] Livermore DM, Walsh TR, Toleman M, Woodford N. Balkan NDM-1: escape or transplant? Vol. 11, The Lancet. Infectious diseases. United States; 2011. p. 164.

[13] Remya P, Shanthi M, Sekar U. Prevalence of blaKPC and its occurrence with other beta-lactamases in Klebsiella pneumoniae. J Lab Physicians [Internet]. 2018;10(4):387–91. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30498308

[14] Cuzon G, Ouanich J, Gondret R, Naas T, Nordmann P. Outbreak of OXA-48-positive carbapenem-resistant Klebsiella pneumoniae isolates in France. Antimicrob Agents Chemother. 2011 May;55(5):2420–3.

[15] Rodriguez-Martinez JM, Cano ME, Velasco C, Martinez-Martinez L, Pascual A. Plasmid-mediated quinolone resistance: an update. J Infect Chemother Off J Japan Soc Chemother. 2011 Apr;17(2):149–82.

[16] Poirel L, Cattoir V, Nordmann P. Plasmid-mediated quinolone resistance ; interactions between human , animal , and environmental ecologies. 2012;3(February):1–7.

[17] Nolivos S, Cayron J, Dedieu A, Page A, Delolme F, Lesterlin C. Role of AcrAB-TolC multidrug efflux pump in drug-resistance acquisition by plasmid transfer. Science (80-) [Internet]. 2019 May 24;364(6442):778 LP – 782. Available from: http://science.sciencemag.org/content/364/6442/778.abstract

[18] Soto SM. Role of efflux pumps in the antibiotic resistance of bacteria embedded in a biofilm. Virulence [Internet]. 2013/02/04. 2013 Apr 1;4(3):223–9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23380871

[19] Patwardhan RB, Dhakephalkar PK, Chopade BA, Dhavale DD, Bhonde RR. Purification and Characterization of an Active Principle, Lawsone, Responsible for the Plasmid Curing Activity of Plumbago zeylanica Root Extracts. Front Microbiol [Internet]. 2018 Nov 8;9:2618. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30467495

[20] Lee L han. An insight of traditional plasmid curing in Vibrio species. 2015;6(July).

[21] Molnár J, Mándi Y, Spengler G, Haszon I, Turi S, Kásler M, et al. Biochemistry & Pharmacology : Open Access Synergism between Antiplasmid Promethazine and Antibiotics In Vitro and In Vivo. 2014;3(4).

[22] Letchumanan V, Chan KG, Lee LH. An insight of traditional plasmid curing in Vibrio species. Front Microbiol [Internet]. 2015 Jul 17;6:735. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26347714

[23] Pulcrano G, Pignanelli S, Vollaro A, Esposito M, Iula VD, Roscetto E, et al. Isolation of Enterobacter aerogenes carrying blaTEM-1 and blaKPC-3 genes recovered from a hospital Intensive Care Unit. APMIS. 2016 Jun;124(6):516–21.

ISSN: 0005-2523
Volume 63, Issue 02, February, 2023

[24] Bharathan S, Sundaramoorthy NS, Chandrasekaran H. Sub lethal levels of platinum nanoparticle cures plasmid and in combination with carbapenem , curtails carbapenem resistant Escherichia coli. Sci Rep [Internet]. 2019;(March):1–13. Available from: http://dx.doi.org/10.1038/s41598-019-41489-3

[25] Vardevanyan PO, Antonyan AP, Parsadanyan MA, Torosyan A, Karapetian AT, Vardevanyan PO, et al. Joint interaction of ethidium bromide and methylene blue with DNA . The effect of ionic strength on binding thermodynamic parameters. 2016;1102(July).

[26] Kalayci S, Demirci S, Sahin F. Antimicrobial Properties of Various Psychotropic Drugs Against Broad Range Microorganisms. Curr Psychopharmacol. 2015 May 20;04:1.

[27] Dastidar SG, Kristiansen JE, Molnar J, Amaral L. Role of Phenothiazines and Structurally Similar Compounds of Plant Origin in the Fight against Infections by Drug Resistant Bacteria. 2013;58–72.

[28] Buckner MMC, Ciusa ML, Piddock LJ V. Strategies to combat antimicrobial resistance : anti-plasmid and plasmid curing. 2018;2013(March):781–804.

[29] Lavanya B, Sowmiya S, Balaji S, Muthuvelan B. Plasmid Profiling and Curing of Lactobacillus Strains Isolated from Fermented Milk for Probiotic Applications. 2011;3(2):95–101.

[30] Letchumanan V, Pusparajah P, Tan LTH, Yin WF, Lee LH, Chan KG. Occurrence and Antibiotic Resistance of Vibrio parahaemolyticus from Shellfish in Selangor, Malaysia. Front Microbiol. 2015;6:1417.

[31] Rohimatun, Wiratno. Potensi dan Prospek Daun Encok (Plumbago zeylanica L.) sebagai Bahan Aktif Pestisida Nabati. 2013;

[32] Srivastava P, Wagh RS, Puranik N V, Puntambekar HM, Jahagirdar SS, Dhakephalkar PK. In vitro plasmid curing activity of aqueous extract of Terminalia chebula fruit against plasmids of Bacillus subtilis and Shigella sonnei. 2015;7(4).

[33] Sharma M. Lytic bacteriophages: Potential interventions against enteric bacterial pathogens on produce. Bacteriophage [Internet]. 2013 Apr 1;3(2):e25518–e25518. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24228223

[34] Bertozzi Silva J, Storms Z, Sauvageau D. Host receptors for bacteriophage adsorption. FEMS Microbiol Lett [Internet]. 2016 Jan 10;363(4). Available from: https://doi.org/10.1093/femsle/fnw002

[35] Lin DM, Koskella B, Lin HC, Lin DM, Lin HC, Gastroenterology S. Phage therapy : An alternative to antibiotics in the age of multi-drug resistance. 2017;8(3):162–73.

[36] Tagliaferri TL, Jansen M, Horz HP. Fighting Pathogenic Bacteria on Two Fronts: Phages and Antibiotics as Combined Strategy [Internet]. Vol. 9, Frontiers in Cellular and Infection Microbiology . 2019. p. 22. Available from: https://www.frontiersin.org/article/10.3389/fcimb.2019.00022

[37] Altamirano FLG, Barr JJ. crossm Phage Therapy in the Postantibiotic Era. 2019;32(2):1–25.

[38] Brown R, Lengeling A, Wang B. Phage engineering : how advances in molecular biology and

synthetic biology are being utilized to enhance the therapeutic potential of bacteriophages. 2017;5(1):42–54.

[39] Bazan J, Całkosiński I, Gamian A. Phage display--a powerful technique for immunotherapy: 1. Introduction and potential of therapeutic applications. Hum Vaccin Immunother [Internet]. 2012/08/21. 2012 Dec 1;8(12):1817–28. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22906939

[40] Wu C hsun, Liu I ju, Lu R min, Wu H chung. Advancement and applications of peptide phage display technology in biomedical science. J Biomed Sci [Internet]. 2016;1–14. Available from: http://dx.doi.org/10.1186/s12929-016-0223-x

[41] Kalafatovic D, Giralt E. Cell-Penetrating Peptides : Design Strategies beyond Primary Structure and Amphipathicity. 2017. 1–38 p.

[42] Jalasvuori M, Friman VP, Nieminen A, Bamford JKH, Buckling A. Bacteriophage selection against a plasmid-encoded sex apparatus leads to the loss of antibiotic-resistance plasmids. Biol Lett. 2011 Dec;7(6):902–5.

[43] Ojala V, Laitalainen J, Jalasvuori M. Fight evolution with evolution: plasmid-dependent phages with a wide host range prevent the spread of antibiotic resistance. Evol Appl. 2013 Sep;6(6):925–32.

[44] Nale JY, Redgwell TA, Millard A, Clokie MRJ. Efficacy of an Optimised Bacteriophage Cocktail to Clear Clostridium difficile in a Batch Fermentation Model. Antibiotics [Internet]. 2018;7(1). Available from: https://www.mdpi.com/2079-6382/7/1/13