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Abstract

This paper reviews the antibacterial potential of enzybiotics against Methicillin-resistant Staphylococcus aureus (MRSA). Due to the increasing occurrence of antibiotic resistance, researchers are looking to make use of the natural antibacterial qualities of virus bacteriophages, viral derived lysins, and antimicrobial peptides to fight MRSA infections. The efficacy of bacteriophages, endolysins, and bacteriocins as potential antibacterial agents against MRSA was extensively researched through Touro's online library database. Each of their mechanisms of action allows them to effectively lyse S. aureus cells, by essentially disrupting the peptidoglycan in the cell wall, causing it to burst. The narrow host range of these antimicrobials causes eradication of only pathogenic bacteria while maintaining the state of normal flora. Researchers have tested the ability of bacteriophages to effectively eliminate MRSA and have experimentally created therapeutically effective phage cocktails to delay the development of bacterial resistance. Different in-vitro and in-vivo studies demonstrate the ability of endolysins to rapidly kill S. aureus regardless of their metabolic state. Truncated and chimeric endolysins are used to optimize certain endolysin properties while eliminating negative ones. The therapeutic use of bacteriocins has significantly reduced and even completely eradicated MRSA infections in rabbit and mice in-vivo studies. Additionally, bacteriocins display synergy when used along with endolysins. All areas of enzybiotics show synergy with antibiotics when both treatments are combined. Additional research must be done before bacteriophages, endolysins, and bacteriocins can be used as a new antibacterial agent against MRSA.

Introduction

One of the greatest medical discoveries was the discovery of antibiotics in the 20th century, which caused the mortality rate of patients suffering from infectious diseases to drop dramatically. Other methods of treating bacterial infections were available at that time but were discontinued after the use of antibiotics became prominent. There are two major disadvantages to the use of antibiotics, the first being that aside from killing the unwanted bacteria they also kill the beneficial ones. The second is antibiotic resistance. Antibiotic resistance occurs when bacteria evolve mechanisms that protect themselves against the effects of antibiotic drugs. With a major misuse of antibiotics globally, antibiotic-resistant bacteria are quickly increasing each year. The discovery of new classes of antibiotics has been slow and is not keeping up with the rapid increase of resistant bacteria. This is causing common infections to become untreatable and once again deadly (Matilla, et. al. 2015).

An example of this is Staphylococcus aureus, a gram-positive, round-shaped bacterial pathogen that is responsible for many infections including bacteremia, pneumonia, sepsis, and wound and bloodstream infections. It is quickly becoming resistant to more and more forms of antibiotics which are making it increasingly difficult to cure. Methicillin-resistant staphylococcus aureus (MRSA) is a group of S. aureus isolates resistant to methicillin as well as many other kinds of antibiotics. Vancomycin is one antibiotic that is used to treat MRSA however vancomycin-resistant MRSA strains have started to emerge (Jensen, et. al. 2015). The inability to effectively treat MRSA has led to a resurgence in attempts to use previously neglected antibacterial therapies to treat it. This review is aimed at researching enzybiotics as one alternative method to treating MRSA infections

Methods

This study was performed through the analysis of various original and peer-reviewed articles which were accessed from Touro's online database including Proquest, PubMed, and Plos One databases. The articles were critically read analyzed and compared to determine the efficacy of enzybiotics as a possible treatment against multi-drug resistant MRSA.

What are Enzybiotics?

Enzybiotics fight bacterial infections through the use of virus bacteriophages, viral derived lysins or antimicrobial peptides. Some advantages enzybiotics have over regular antibiotics are their different mechanisms of killing bacteria, including antibiotic-resistant bacteria. Most importantly, the use of certain enzybiotics has not resulted in new development of bacterial resistance. For these reasons, enzybiotics represent a promising alternative to traditional antibiotic use by complimenting as well as replacing antibiotics in treating bacterial pathogenic infections including MRSA.

Originally, Enzybiotics referred to designated bacteriophage enzymes provided with the ability to break down cell walls which could be used as antimicrobial agents. However, eventually, enzybiotics began referring to all enzymes that displayed antibacterial or antifungal activity.

Bacteriophages

Bacteriophages are viruses that insert their genetic material into bacteria in order to replicate. The tails of phages bind to receptors found on the surface of bacteria allowing them to inject the DNA into the bacterial cell. For virulent phages, DNA replication produces many new phages which burst from the host cell and kill it. These replicated phages now move onto the next bacterial cell and repeat the process (Thurber, 2009). Their characteristic of being

able to replicate at the site of infection and therefore be available in abundance where needed, gives bacteriophages an advantage over traditional antibiotics (Gu, et. al. 2012).

Binding to a specific receptor is required for bacteriophages to infect bacteria, making phages extremely host-specific. Due to their narrow host range, using phages to treat infections is advantageous, because phage treatment can focus accurately on the pathogen infecting human cells while not harming normal flora. For this reason, there are thought to be minimal side effects associated with phage therapy (Jensen, et. al. 2015).

Phage therapy has been used previously in the early 20th century, however, when antibiotics were discovered, research in the phage treatment ended. Now that antibiotics are beginning to fail and there is a major need for alternatives, phage therapy is being looked at as a possible option (Mattila, et. al. 2015). Although bacteria can become resistant toward phages as well, phage therapy can possibly be a greater option because of its ability to change in response to the development of resistance by target bacteria.

Nosocomial infections are infections that are contracted within a hospital environment. Transmission of these infections often occurs via hospital equipment and fomites that are not properly disinfected. This is a common way that MRSA infections get transmitted and is a major concern amongst immunocompromised patients in hospitals. Researchers have studied the ability of phages to successfully decontaminate fomites associated with nosocomial transmission. Glass coverslips were used to represent decontamination of solid surfaces and cloth from a lab coat to represent the coats worn by clinicians.

Strains of S. aureus were isolated from many sources such as human nasal swabs, hospitals, dog hair, and poultry. Isolated phages were able to significantly reduce the colony-forming units of MRSA from the surfaces of the glass and fabric. They tended to demonstrate greater lytic activity toward the MRSA strains isolated from human sources. They were able to isolate at least six different phages that displayed lytic activity against human MRSA isolates and were able to decontaminate hard surfaces as well as fabric surfaces (Jensen, et. al. 2015).

Phage Cocktails

Phage therapy isn't infallible because bacteria have been shown to develop resistance towards phages. In attempt to solve this, the use of phage cocktails was studied. Phage cocktails are when multiple phage types each possessing different host ranges are combined. Studies have shown that using this method delays the development of phage resistant variants. However, it is difficult to acquire a set of phages that are effective against all variants of a specific bacteria, and if too many different phages are used in effort to increase the host range the therapeutic efficiency of the cocktail decreases.

Researchers have studied the possibility of creating patient-specific phage cocktails containing phages specific for the infection present. Compared to pre-made cocktails, this method of tailored phage cocktails ensures that unnecessary phages aren't used. For this method of treatment to be possible, hospitals would be required to have access to a large variety of phages at all times so that when a pathogen is identified they can obtain the specific phages that are effective against it.

The probability of successfully isolating phages effective against common hospital-acquired bacterial infections on demand was experimentally tested. Researchers found that the probability of finding phages from sewage, an optimal resource of phages, varied greatly for different host bacterium. Out of a total of 117 attempts, phages for only a single strain of S. aureus were discovered. After continuing to investigate whether alternative sources would be more suitable for obtaining phages effective against MRSA, only phages for strain SA10 of S. aureus were found. This specific study concluded that creating personalized phage cocktails on demand is not possible for treating MRSA like it is for other common infections. To treat these infections using this method, pre-made wide range cocktails would have to be used. (Mattila, et. al. 2015).

Phages cocktails were also used to determine their potential synergistic ability to decontaminate fomites. The difference is that the phages used weren't required to be extremely specific. Results of this study showed that the cocktails were effective in decontaminating both the lab coat fabric and the glass coverslips (Jensen, et. al. 2015).

Combination of Phage and Antibiotic Therapy

One way to use bacteriophages to combat infections is to combine phage therapy with antibiotic therapy. The combination of both antimicrobial agents seems to be synergistic; the interactions between both antimicrobial agents create a combined effect that is greater than than each of their individual effects. Not only has using this combination therapy shown to be helpful in effectively controlling bacteria, but studies have shown that phage therapy used along with antibiotics prevents the development of resistant strains. Therefore, using methods of combined treatment of bacteriophages with antibiotics can be effective in helping to resolve the issue of antibiotic resistance (Torres-Barceló, et. al. 2016).

S. aureus is one of the most common pathogens found in diabetic foot infections. Overuse of antibiotics to treat

these infections resulted in MRSA accounting for almost half of the S. aureus isolates found in diabetic foot infections. It's estimated that at least 50% of deaths caused by diabetic foot infections are because of strains that were antibiotic resistant and therefore untreatable. One available alternative treatment option is linezolid, an antibiotic that is known to cure diabetic foot infections without causing major side effects. Researchers have attempted to used phage therapy along with linezolid to treat induced foot infections in diabetic mice. To test their synergy, they used phage MR 10 alone and in combination with linezolid.

Results of the study demonstrated that in a group of mice that received an injection of phage MR 10, the infection was completely resolved after seven days. However, greater results were observed in a group of mice that were administered both phage MR 10 and linezolid. There, the infection was also completely resolved by day seven but there were comparatively lower bacterial loads on each day when compared to treatment with phage 10 alone. This showed that phage given along with linezolid were synergistic in controlling the pathogen population. Linezolid prevented further growth of the pathogen because it is a bacteriostatic antibiotic, and phage 10 killed the already existing bacterial population (Chhibber et. al., 2013).

Endolysins

A major disadvantage to phage therapy is the ability of bacteria to develop resistance to the phages. Because of this, researchers have looked into the possibility of purifying the lysins from bacteriophages to be used separately as antimicrobial agents. Holin and lysin are two proteins that allow reproduced phages to exit the infected bacterial host cell. The holin creates pores in the cytoplasmic membrane and allows the endolysin to access the peptidoglycan in the cell wall of the bacteria. This causes water to flow into the cell, resulting in its rupture, and release of the replicated phages. Because of their properties endolysins are being studied as possible antimicrobial agents that when applied to pathogenic gram-positive bacteria attack the peptidoglycan and lyse the cell wall (Pastagia, et. al. 2013).

Cell walls of S. aureus are primarily composed of peptidoglycan, teichoic acids, and different surface proteins. Peptidoglycan is a structural polymer that is composed of glycan chains of repeating N-acetylglucosamine and N-acetylmuramic acid that are cross-linked with peptide side chains (Vacek, et. al. 2020). Peptidoglycan hydrolases are often specific to certain species and genera since their peptidoglycan structures vary. Consequently, the use of phage endolysins as antimicrobials can help provide a targeted therapeutic approach, without killing unrelated commensal bacteria. It could also be useful in avoiding the use of broad range antibiotics which often cause the development of resistance (Becker, et. al. 2009).

LysK

Phage endolysins are found to have two or three domains. One or two N-terminal catalytic domains and a C-terminal cell wall binding domain. LysK is an endolysin derived from staphylococcal bacteriophage K, a phage that has proven to kill a broad range of pathogenic staphylococci. LysK is characterized as an endopeptidase, an enzyme that breaks peptide bonds. It contains three domains, two N-terminal catalytic domains, cysteine, histidine-dependent amidohydrolase/peptidase (CHAP) domain, an amidase-2 domain, and one c-terminal SH3B cell wall binding domain. LysK has shown to have the ability to kill MRSA without permitting bacterial resistance to develop.

In one specific study, researchers attempted to determine whether all three domains found on LysK were necessary for it to perform exolysis (lysis from outside the cell). Analysis of their activity indicated that the CHAP domain is sufficient for exolysis of S. aureus cells but it's activity was enhanced greatly when the SH3b domain was present (Becker, et. al. 2009).

Researchers have cloned and expressed LysK in Lactococcus lactis to test whether it can inhibit a range of different staphylococci species including MRSA. Results confirmed that the recombinant LysK had the ability to degrade staphylococci cell walls. It was found to be active against a variety of live staphylococci, including MRSA strains from Irish hospitals. Gram-positive bacterial strains from other genera were not affected by the lysates containing LysK, suggesting that LysK is specific to staphylococcus. These results suggest that LysK could have widespread applications as a therapeutic agent against staphylococci infections including MRSA (O'Flaherty, et. al. 2005).

CF-301

CF-301 is another example of a lysin that demonstrates activity against S. aureus. In one particular study, CF-301's activity was examined alone and in combination with standard-of-care (SOC) antibiotics. It was tested in vitro against laboratory and contemporary clinical strains of MRSA, and in vivo against MRSA-induced murine bacteremia.

CF-301 killed S. Aureus rapidly both in vitro and in vivo. Its rate of antimicrobial activity in vitro was found to be a lot faster than that of the SOC antibiotics. CF-301 began killing MRSA laboratory strains within 30 minutes in contrast to the antibiotics, which required six hours to reach the same point. The same results were true when CF-301 was used to treat MRSA-induced mice. MRSA CFU (colony forming unit) was tested in their blood prior to and post

treatment. They found that after just 15 minutes there was a large decrease in CFU and even more after an hour. This rapid killing property of lysins makes them well suitable to quickly reduce the bacterial load in infected hosts.

Aside from its activity alone, CF-301 exhibited synergy when combined with SOC antibiotics both in vitro and in vivo. The synergy between the lysin and antibiotics was assessed in three different ways. First with a time-kill assay that studies the activity of antimicrobial agents against bacteria over time. Two antibiotics, daptomycin, and vancomycin were tested alone and in combination with CF-301. Sub-MIC levels (minimal inhibitory concentration) of lysin demonstrated synergy with sub-MIC levels of the two tested antibiotics. To confirm synergy, a checkerboard assay was also used. When CF-301 treatment was combined with the two antibiotics it was more effective at killing the majority of the tested MRSA strains than when each treatment was used alone. A third method was used which further confirmed these findings by showing that when in the presence of CF-301 the MIC levels of the antibiotic majorly decreased.

Additionally, there was little to no resistance of S. aureus to CF-301 seen after treatment for 26 days, compared to high bacterial resistance of S. aureus to SOC antibiotics which were 128 and 16 times the initial MIC. When the two treatments were combined and MRSA was treated with increasing concentrations of antibiotics in the presence of sub-MIC CF-301 for twenty-eight days, there was only a 4- fold increase in their resistances. These results demonstrate that the presence of the lysin suppressed the formation of antibiotic resistance.

Mice with staphylococcal-induced bacteremia were treated with CF-301 and daptomycin together and separately, in low and high challenge models. In some of the studies, the lysin yielded a higher survival of the mice and in others the antibiotics did, but, in all the cases the survival rate yielded from the combination treatment significantly outperformed the treatments with each of them alone.

These results can have clinical implications when designing new treatments using combinations of lysins and antibiotics. Because CF-301 proved to act fast, it would quickly reduce the burden of the pathogenic bacteria, while the antibiotic would act on the remaining bacteria. Additionally, when the bacteria are exposed to small amounts of lysin, which break the bonds of peptidoglycan, it causes the bacterial structure to become more permeable which allows for the antibiotic to penetrate more easily (Schuch, et. al. 2014).

Endolysins and Biofilm Eradication

S. Aureus forms biofilms within infected tissue which help them grow and survive in the presence of antibiotics and the immune system. Biofilm infections tend to develop in patients with prosthetic objects implanted into their bodies. They are harder to treat than free-living bacteria, and even more so biofilms of antibiotic-resistant pathogens such as MRSA (Chopra, et. al. 2015a). These biofilms are difficult to destroy because of their altered metabolic activity as well as the presence of an extracellular matrix making them difficult to penetrate (Rani et al, 2007).

Researchers attempted to test the efficiency of phage lysins in eradicating old and new biofilms formed by MRSA, possessing or lacking ica-locus. Phage-borne endolysin MR-10 was tested alone and in conjunction with minocycline. First, both kinds of biofilms were treated with endolysin MR-10 alone. They found that the optimum concentrations for eradicating young ica-negative MRSA biofilm was 18 g/ml, and for ica-positive MRSA biofilms, 36 g/ml. Here, the difference in intracellular adhesion seemed to affect the optimum concentrations needed.

The effectiveness of any antimicrobial agent against biofilms is largely determined by the age of the biofilm. Young biofilm formed by ica-negative and positive MRSA can be controlled by using the antibiotic minocycline alone at high concentrations, however, once the biofilm gets older the minocycline becomes ineffective (Chopra, et. al. 2015b). Since any lysin concentration was ineffective against completely eradicating mature biofilm, minocycline was used at its highest concentrations together with endolysin MR-10, in an attempt to completely eradicate the biofilm. No significant decreases were observed when equal concentrations of endolysin MR-10 and minocycline were used. The researchers believe the reason for this is because both agents worked together on the top layers of the biofilm and did not reach the interior. It is known that antibiotics are unable to penetrate deep into biofilms because of their complex matrix structure, and since lysins are one-use enzymes it's possible that both agents bound to the same cells resulting in little activity against them.

To test this theory, the researchers studied if sequential treatment of both page endolysin MR-10 and minocycline would have positive results in eliminating older MRSA biofilm. Two sequences were studied and each had different results. First, they exposed the biofilm to endolysin MR-10 for six hours and then treated it overnight with minocycline. A decrease in mature biofilm was observed to some extent after being treated using this method. However, when the biofilm was first treated which minocycline for three hours followed by endolysin MR-10 overnight there was a more significant decrease in cell count of the mature biofilm.

The reasons for these results are as follows. Antibiotic can not penetrate the layers of the biofilm and is only effective against the active cells so when the antibiotic was used first it was able to kill the metabolically active cells which are found at upper layers if the biofilm. Since endolysins are effective against bacteria regardless of their metabolic activity and have low molecular weights, endolysin MR-10 was able to penetrate more effectively into the deeper layers of the biofilm which the antibiotics could not reach. This study provides important research that lysins have the potential as an antimicrobial agents in the eradication of MRSA biofilm. Its mode of action targets the bacteria peptidoglycan and does not require the bacterial cells to be metabolically active which is unlike antibiotics (Chopra, et. al. 2015b).

Truncated and Chimeric Endolysins

Because endolysins have modular structures, domains can be swapped or removed to create newly combined lysins that have altered catalytic activities and binding specificity. Doing so can optimize different properties lysins have and eliminate possible downsides such as low solubility and poor expression in heterologous hosts.

CHAPk is a truncated single domain lysin that has been used experimentally to eliminate S. aureus from the nostrils of artificially infected mice. It demonstrated high solubility, rapid lytic activity, and high specificity against S. aureus. A single treatment with CHAPk greatly reduced the bacteria after just one hour. Using this enzyme may be an effective way to eliminate MRSA colonization in the human nares.

The human nostril is the most frequent carriage site of S. aureus which often serves as a reservoir for the spread of the pathogen. It had been found to play a vital role in the development of S. aureus infections, particularly in immunocompromised patients. Because CHAPk has the potential to quickly reduce the reservoir, it can be valuable in the prevention and spread of life-threatening MRSA infections. This is a property that is not found in antibiotic topical treatments which often take a couple of days to effectively remove S. aureus (Fenton, et. al. 2010).

In a different study, the catalytic domains of two highly soluble E. faecalis phage endolysins were fused with the c-terminal cell wall binding domain of the staphylococcal phage endolysin, Lys87. Two different chimeric endolysins were created in hopes to solve the problem of low solubility. The combined endolysins were able to efficiently lyse 96% of the 143 S. aureus clinical isolates that were tested. Included in the clinical isolates were strains of MRSA that represented some of the most relevant MRSA epidemic clones. The MRSA strains showed to be susceptible to both of the chimeric endolysins.

Aside from showing activity against Staphylococcus, the combined endolysins showed a broadened lytic activity towards enterococcus as well. This demonstrates that engineering chimeric endolysins can be a good way of obtaining soluble and highly effective peptidoglycan hydrolyses that have a broad lytic spectrum (Fernandes, et. al. 2012).

Bacteriocins

Bacteriocins are antibacterial proteins produced by non-pathogenic bacteria that inhibit the growth of closely related bacterial strains (Farkas-Himsley, 1980). They have relatively narrow spectra of antimicrobial activity due to being directed primarily toward bacterial strains closely related to their producing strain. Bacteriocins make up a family of proteins comprised of many different types, each exhibiting different properties (Hanchi, et. al. 2017).

Lysostaphin

Lysostaphin is a bacteriocin that is secreted by Staphylococcus simulans, a gram-positive bacteria. Lysostaphin possesses the ability to lyse a staphylococcus bacterial cell by disrupting its peptidoglycan layer (Schindler, Schuhardt, 1964). The major substrate for lysostaphin is the pentaglycine interpeptide bridge (Bowder, et. al. 1965). Since this is an obvious feature of the cell wall of S. aureus, lysostaphin can selectively target it, thereby killing the bacteria. Lysostaphin cleaves the staphylococci cell wall between two amino acids in the pentaglycine cross bridge. By cleaving these amino acids the lysostaphin destabilizes the bacterial cell wall causing a loss of osmotic equilibrium which ruptures the cell (Zygmunt, et. al. 1972).

Purifying, as well as cloning the lysostaphin gene into different expression systems has led to creating a highly purified recombinant lysostaphin with high specific activity. The availability of this recombinant as a potential antimicrobial agent against S. Aureus has become of interest as new methods are being researched to combat bacterial resistance.

Durancin 61A is a bacteriocin produced by Enterococcus durans which is also being studied as a possible treatment against MRSA. It has been found to exhibit antibacterial activity when tested in vitro (Hanchi, et. al. 2017).

Lysostaphin Antimicrobial Activity in Vivo

Multiple studies have researched the use of recombinant lysostaphin in treating S. aureus. One experiment tested its ability to treat S. aureus-induced infections in mice. It was found that administering 5mg/kg of lysostaphin once a day for three days successfully cleared their kidney infections caused by MRSA and significantly reduced their liver and spleen infections. This demonstrates

lysostaphin's ability to penetrate tissue when administered intravenously. Compared to a higher dose treatment over one day, repeated administration of a lower dose of lysostaphin was found to be more effective for the treatment of S. aureus (Kokai-Kun, et. al. 2007).

S. aureus is a leading cause of bacterial keratitis which can result in irreversible damage, e.g. a loss of visual acuity or even complete blindness. Keratitis is normally treated with a topical treatment of antibiotics, such as ciprofloxacin, however more and more MRSA strains have become resistant to it. Lysostaphin was used experimentally to treat bacterial keratitis in rabbits against vancomycin, an antibiotic used to treat MRSA infections. Results demonstrate that lysostaphin is an effective treatment for experimental keratitis caused by S. aureus.

Minimal inhibitory concentrations of lysostaphin were determined for multiple strains of MRSA and were found to be many times lower than the MIC's of vancomycin. In addition, Lysostaphin successfully sterilized the rabbit corneas when treated early on in the infection, compared to vancomycin which did not completely sterilize them. When treated later on in infection, although lysostaphin did not completely sterilize the corneas, it reduced the CFU (colony forming unit) per cornea more than the vancomycin therapy did when used to treat early in the infection.

Just like endolysins, bacteriocins share the property remaining effective regardless of the metabolic status of the bacterial cells. They can kill both rapidly growing cells as well as non-dividing cells. Through experimentation, lysostaphin proved to be an effective therapy during the late stages of the staphylococcal infection when there is minimal bacterial replication. This gives bacteriocins an advantage over most antibiotics to which this is an unusual characteristic.

Infected eyes that were treated were found to be free of detectible pathological changes after being observed for seven days. Lysostaphin did not cause any conjunctival inflammation or corneal edema as did vancomycin. However, further studies are needed to determine whether there are any adverse effects caused by repeated uses of topical lysostaphin since it has the potential to cause an immune response against itself. The availability of recombinant lysostaphin can help with this issue (Dajcs, et. al. 2000).

Bacteriocin Combination Treatments

Studies have shown that there is a synergistic effect between lysostaphin and antibiotics. When lysostaphin was experimentally used with oxacillin to treat MRSA in vivo it improved its efficiency and allowed for a lower therapeutic dose to be used. Treatment with this method would also be beneficial in preventing the emergence of S. aureus that is resistant to lysostaphin (Kokai-Kun, et. al. 2007).

Researchers have also attempted to combine the treatment of lysostaphin with endolysin LysK. They did so by combining enzymes consisting of both the catalytic domains of LysK and Lysostaphin to treat infections. An experiment that combined the two enzymes demonstrated greater growth inhibition of MRSA then each enzyme showed alone (Becker, et. al. 2009).

Synergy between durancin 61A and vancomycin was observed in inhibition of growth of S. aureus ATCC 700699, a methicillin-resistant staphylococcus strain. By combining the two, each of their MIC levels were reduced drastically (Hanchi, et. al. 2017).

Conclusion

As antibiotic resistance continues to become a more prevalent medical concern, scientists are constantly searching for new effective antimicrobial therapies. Research and experimentation suggest that enzybiotics may serve as possible solutions for combating multi-drug resistant bacteria and particularly for the treatment of MRSA. Each area of enzybiotics provides different advantages over antibiotics, however possible downsides need to be taken into account.

Phage lysins seem to be a favorable way of combating MRSA infections. Their speed of bactericidal activity, low probability of affecting normal flora, as well as the small chances of bacterial resistance, gives endolysins an advantage over traditional antibiotics. Additionally, the use of phage lysins incorporates all the positive aspects of phage therapy without the negative possibility of creating resistant mutations.

Utilizing combination treatments of enzybiotics along with antibiotics is another effective method of combating MRSA. When tested, combination treatments tended to be synergistic and showed the greatest results for killing MRSA than when each therapy was used alone. Each therapy provides its own mechanism of action, so when used together, each provides its specific capability's to effectively combat the bacterial infection.

Despite the growing potential of enzybiotics, further research must be conducted as well as implementing enzybiotics into clinical trials in order to establish enzybiotics as a tried and true therapeutic option for combating MRSA infections.

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