Biotechnological
Communication

Biosci. Biotech. Res. Comm. 12(3): 601-608 (2019)

BBRC
Bioscience Biotechnology
Research Communications

Role of Bacteriocin in Tackling the Global Problem of Multi-Drug Resistance: An Updated Review

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ABSTRACT

Bacterial resistance to antimicrobials has reached an unacceptable level which threatens the very existence of man and animal alike if the situation is not corrected in the near future. The development of novel antibiotics is a slow time consuming process which leaves us with inadequate means to control microbial infections. It is imperative that we adopt alternative therapeutic strategies to ensure removal of resistant micro-organisms from our living space. Bacteriocins are powerful bactericidal peptides produced and secreted by a varied group of micro- organisms including yeast, protozoa and of course bacteria and they cause death and removal of non bacteriocin producing pathogenic bacteria. These bacteriocin treatments offer more benefits over antibiotic therapies in present time as they are natural bioactive peptides having no side effects. This paper is a review of MDR (Multiple rug Resistance) related issues which have become a global problem and on the possible role of bacteriocins as an effective option for fighting against MDR disease causing bacteria. The potential of Bacteriocins as an alternate or adjuvant to antibiotics needs to be studied and made available to the medical community. Recent trends suggest that if an effective alternate to antibiotics is not found quickly then the very existence of mankind could come under threat .The safety profile of bacteriocins is much superior to antibiotics. This is another important reason to study bacteriocins and tap their therapeutic potential to combat drug resistant bacterial infections.

KEY WORDS: ALTERNATIVE THERAPEUTIC STRATEGY, ANTIMICROBIALS, BACTERIOCINS, GLOBAL PROBLEM, MULTI-DRUG RESISTANCE

Article Information:*Corresponding Author:sabiha.fet@mriu.edu.in
Received 3/07/2019 Accepted after revision 24/09/2019
Published: 30th Sep 2019 Pp-601-608

Published by Society for Science & Nature, Bhopal India.
Available at: https://bbrc.in/
Article DOI: http://dx.doi.org/10.21786/bbrc/12.3/8

INTRODUCTION

Microorganism impervious to antibiotic treatment have become wide spread which is a global phenomena needs to be controlled before it becomes a unmanageable deadly threat to the health and wellbeing of human life. The phenomena of antibiotic resistance can be attributed to inappropriate, self medication and excessive prescription of antibiotics over the past several years all over the world according to Carlet et al (2012). Developmentof reasonable alternatives to antibiotics are in need to get universal public health out of danger (Carlet et al., 2012 Oldfield and Feng, 2014 and WHO, 2015). Antimicrobials used in food industries, bio-preservatives or antibacterial peptides like Nisins, pediocin, mersacidin, mutacin and lactacin have proved to be active against Vancomycin Resistant Enterococci and Methecillin Resistant Staphylococcus aureus strains, have instance of potential therapeutic strategy to kill bacterial infections and multidrug-resistant bacteria (Papagianni and Anastasiadou, 2009, Nishie et al., 2012, Bodaszewska-Lubas et al., 2012, Lohans and Vederas 2012, Laxminarayan et al., 2016, Santos et al., 2017, Delpech 2017, Mathur, et al., 2018).

The bacteriocins are very small ribosomally synthesized peptide molecules secreted by archea, gram-positive and some of gram-negative bacteria (Klaenhammer et al., 1988 and Zheng, et al., 2015) as well as synthesized by ribosomes with antimicrobial properties against various groups of microorganisms (Chikindas, et a., 2017). The activity of bacteriocins is influenced by temperature, pH, and composition of culture medium (Guinane et al., 2015 and Turgis, et al., 2016). The bacteriocins were first described in 1925, however their production, functions and applications in medical field has been explored in recent times (Chikindas, et al., 2017). Recently, it has been defined that bacteriocins are secreted not only by bacteria but also by others like yeast and mould, virus, eukaryotic cells like sperm cell, cancer cell and also from protozons (Drider et al., 2016, Jiang, et al., 2016, Chikindas et al., 2017, Mills et al., 2017, Diep, et al., 2018, Lopetuso, et al., 2019).

Bacteriocin has already found commercial application in food preservation and dairy farming therefore it is not far-fetched to assume that Bacteriocins will soon be available for the benefit of humans also this may be as a therapeutic agent against MDR bacteria. They are being investigated as a potential alternative or adjuvant in combination with antibiotics to combat disease causing pathogens. The fact that they have an excellent safety and resistant profile is an added incentive towards studying them. They are considered as therapeutic complements despite therapeutic alternative to chemical antibiotics as they have high stability and very low toxicity.

Advantages of Bacteriocin Treatment over Antibiotic Therapy

Antibiotics are a group of pharmaceuticals that play a vital role in keeping both humans and animals disease free thus having an important influence on the quality of life of an individual (Stepanauskas, 2006). Antibiotic resistance is a growing threat to the efficacy of these agents and has serious consequences in terms of morbidity and mortality of those undergoing treatment (Fair, et al., 2014). Due to the development and dispersal of antibiotic resistance and their several side effects, treatment with antimicrobial peptides is a needed requirement (Chen et al., 2012). Bacteriocins are bacterial extracellular ribosomal integrated peptides or proteins having antibacterial action against closely related microbial species (Tashakor et al., 2017, Castro et al., 2011, Opsata et al., 2010, Morisset and Frère2002). Bacteriocins influence the immune system and inhibit competitive strains by directly influencing the niche competition among commensals (Kommineni, et al., 2015). The bactofencin A or bacteriocin 21 produced by Enterococcus faecalis can eradicate multidrug resistant bacteria and contribute to regulation of niche competition among intestinal bacteria (Kommineni, et al., 2015). Likewise, LAB bacteriocins play role against Staphylococcus aureus (Umu, et al., 2017), some vancomycin resistant enterococci (Kommineni, et al., 2015), Salmonella enteritidis (Umu, et al., 2017), Clostridium difficile (Rea, et al., 2013) and Listeria monocytogenes (Umu, et al., 2017). Additional investigations are required to test the therapeutic potential of above outcomes.The antibacterial properties of bacteriocins are exploited by applications in food technological research. In particular, bacteriocins are used as food preservatives (Oldak, et al., 2017) and preservation of dairy products (Linares, et al., 2017) with categorization such as partially purified bacteriocins, crude-fermented dairy bacteriocins and protective cultures bacteriocins (Henning, et al., 2015, Anacarso, et al., 2017, Chikindas, et al., 2017, Ahmad, et al., 2017, Hammami, et al., 2019).

Mode of Action of Bacteriocin

Most of the bacteriocins can inhibit growth of pathogens in order to defend their producer and play a role in signalling peptides (Hegarty, et al., 2016). They can act as pore-forming agents or membrane perturbers (Etayash et al 2015) or interfere with the cell division processes. The bacteriocins possess antiviral, spermicidal (Chikindas, et a., 2017), anticancer properties (Kaur et al 2015) and capable of enhancing the positive effects of probiotic bacteria as seen in the Bifidobacterium strain (Weinstock, et al., 2016 and Hegarty, et al., 2016).

Different viewpoints distinguish bacteriocins from antimicrobial drugs: (i) Bacteriocins are synthesized on

the ribosomal surface in bacterial cells, while antibiotics are bacterial secondary metabolite; (ii) Antibiotic producers are easily affected by antimicrobial agents whereas the producers of bacteriocin are not susceptible to antimicrobial agents; (iii) Bacteriocins can get fixed to the target bacterial cell surface anywhere because target bacterial cell surface doesn't possess any specific receptors; iv) Bacteriocins get attached to the target cell wall surface and form pore in the outer membrane surface because of ionic imbalances (Morisset and Frère, 2002) another side chemical antimicrobials are responsible for disruption of cell wall (bacterial) synthesis, formation of genomic protein and replication processes (Svetoch et al., 2011, Cotter et al., 2013, da Silva Sabo et al., 2014, Woraprayote et al., 2016, and Perez et al., 2018).

Emergence of Bacterial Resistance to Antibiotic

The resistant bacterial microorganisms are acquired by human being through consumption of animal meat. These bacteria show changes at the gene level which plays a role in them acquiring resistance to antibiotics. Consequently the consumer of such meat becomes insensitive to the action of antibiotics involved (Ventola, 2015, Holmes, et al., 2016, Chakchouk-mtibaa, et al., 2017, Vijayakumar and Muriana, 2017, Costa, et al., 2019).

Bacterial resistance emerges and propagates due to the reasons listed below:

1. Excessive consumption of antibiotics: Over utilization of antibiotics leads to multiple drug resistance which invariably selects the resistant species of normal flora. The excessive utility of those medicines might be due to lack of information or overzealous and sometimes even profit driven treatment for various viral and bacterial infections (Nitsch-Osuch et al., 2016).
2. Overprescribing of antibiotics: Apart from excessive consumption, the number of inappropriate prescriptions of antimicrobial agents is also shocking. It has been found that there are errors of about 30 - 50 % in terms of choice and duration for which the antibiotics need to be consumed (Ventola, 2015). It has been observed that the sub therapeutic doses of antibiotics promote bacterial phenotypical variations and resistance to bacterial infections builds up (Viswanathan, 2014).
3. Antibiotic use in agronomy as well as animal husbandry: It was observed that in 2011 in the US, the use of antimicrobials as a growth enhancer in livestock was approximately 13,000 tons. That year more than 42,000,000 tons meat was produced which was an average of at least 320 mg of the bactericidal per kilogram of meat (Aarestrup, 2015).

Research Regarding Bacteriocin's Effect on Multi Drug Resistance Bacteria

Researchers from Howard University Washington DC have shown that probiotic isolate from yogurt has strong antimicrobial activity. Among the multiple *Lactobacillus* isolated and studied one particular isolate *Lactobacillus parafarraginis*, was reported to be sensitive against fourteen multi drug resistant bacteria (Allen-McFarlane et al., 2019).

Recently, the bacteriocins from *Vibrio, Aeromonas, Pseudoal-teromonas* and *Alteromonas* were sourced from the ocean and were noted to have high bactericidal activity. They provide defence system against multidrug-resistant bacteria by establishing bacteriocins. The system is found to be reasonable alternatives to antibiotics for high biodiversity of the ecosystem (Desriac et al., 2010).

On the contrary, Sachsenrödder et al. (2014) postulated that the administration of probiotics (bacteriocins from *Enterococcus faecium*) to diarrhoea causing virus in pig gut would be therapeutic but they failed to prove the same through actual results (Sachsenrödder et al., 2014). Previous study also showed that pyocin, a bacteriocin produced by *Pseudomonas aeruginosa* were not able to treat pulmonary disease caused by pseudomonas in patients (Ghoul et al., 2015) Bacteriocin isolated from *Bacillus subtilis* that have been used to increase shelf life of food items have showed activity against only a very few gram positive bacteria like *S. epidermidis*. They failed to show activity against any drug-resistant bacteria (Sharma et al., 2018) Studies have been also conducted on AS 48 and nisin, a bacteriocin from *Lactococcus lactis* with AS48 being effectively bactericidal against *Staphylococcus* in cereal drink only when those are combined with phenol compounds (Antonio, et al., 2019).

Researchers from Leuven Belgium have studied the mode of action of LipA bacteriocin which helps to kill multidrug-resistant *Pseudomonas aeruginosa*. Their work has shown that the bacteriocin is both effective and very specific in targeting the pathogenic organism (Martín-Escolano, et al., 2019).Perales-Adán J, et al (2018) had shown the bactericidal action of bacteriocins (AS-48 and nisin) against drug-resistant *Staphylococcus aureus* present in goat milk cheese both individually and in combination. The combined action of these bacteriocins is even more effective because of synergy (Perales-Adán, et al. 2018). Scientists from Pakistan have studied the BAC-IB-17 bacteriocin produced by *Bacillus subtilis* and wasfound it to be effective against MRSA. This bacteriocin was highly thermo stable and therefore would retain its activity in a range of extreme environments (Ansari, et al., 2018).

Indian researchers from CSIR- Institute of Microbial Technology, Chandigarh, have shown that the bacteri-

ocin 'Sonorensin' is effective against antibiotic-resistant *staphylococcus aureus* biofilms and other bacteria of gram- positive and gram- negative types (Chopra, et al., 2015).

Five antimicrobial peptides are designed by Indian Institute of Science, Bangalore scientists.The peptide Ω76 which is among the five peptides was effective against carbapenem and tigecycline-resistant *Acinetobacter baumannii* in mice. The peptides are nephrotoxic lead to side effects in patients which may be treated with conventional antibiotics (Nagarajan, et al., 2019). A scientists' team from China studied antimicrobial peptide Cec4 for its structure and mode of action.The peptide is effective against the drug-resistant nosocomial infections caused by *A.baumanii* (Peng, et al., 2019).

A team of scientists at MIT has discovered a peptide from the venom of a South American wasp. They successfully developed and refined several variants of this peptide and tested their efficacy in mice infected with Antibiotic-resistant *Pseudomonas areuginosa*. Among all the peptides tested one peptide was seen to eradicate the infection- an encouraging and interesting result (Marcelo, et al. 2018). The bactericidal actions of bacteriocins were studied VidhyaPrakash et al. which were produced by *L. fermentum* and *L. casei* 335 showed effective against antibiotic-resistant Escherichia coli and also drug resistant *Salmonella typhi* bacteria. This study showed that both the pathogenic bacteria were inhibited by bacteriocin action (Prakash, et al. 2018). Also in our research we have found a bacteriocin producing lactobacillus which is very much effective against Methicillin resistant *Staphylococcus aureus* (Bonhi and Imran, 2019).

MDR Bacteria and Antibiotic Resistance – The Global Scenario

According to report published by UN in April 2019, there may be loss of lives every year numbering up to 1,00,00,000 caused by drug resistant diseases by 2050. The causality may be similar to disastrous economic loss during 2008-09. Antimicrobial resistance may lead to 24 million into extreme poverty by 2030.Drug resistant infections lead to death of minimum of 7,00,000 individuals every year. Tubercle bacilli multidrug-resistant infection lead to death of 2,30,000 additionally. Sexually transmitted infections, Urinary tract infections and common respiratory tract infections are untreatable in present context. The treatments meant for life saving became risky and modern food systems are increasingly uncertain (Chaib, et al. 2019).

The prevalence of carbapenems degrading enzymes New-DelhiMetallo-beta - lactamase-1 and *Klebsiella pneumonia* carbapenemase-2 are matter of concern to the researchers for treatment of infectious diseases due to inadequacy of antibiotics (Liu et al., 2016). The "One Health" approach of UN recommends countries to redress antimicrobial resistance and to ensure efficacy for essential medicines by framing strategic plan for deployment activities like finance and arranging awareness programs for prudent use of antimicrobials.It insists to invest in research and development for new technologies to combat antimicrobial resistance and growth of critically essential antimicrobials in agriculture (Chaib, et al. 2019).

MDR Bacteria and Antibiotic Resistance – The Indian Scenario

The problem of Antibiotic resistance has assumed serious proportions in India too. Findings from a study published by ICMR show the presence of antibiotic resistant bacteria in the digestive system of 2 out of every 3 individuals tested thus confirming the high prevalence and spread of Antibiotic resistance in Indian population. The resistance was more for frequently used antibiotics like cephalosporins (60 %) and flouroquinolones (40%). This study is a wakeup call for the future because a similar resistance for higher end antibiotics would be disastrous. Of even more concern is the threat of Drug resistant tuberculosis. The Central TB division is found with declaration furnished in 2018 by Ministry, Health and Family Welfare.As per the declaration, there were approximately 2.8 million new cases of TB every year and 1,47,000 new cases of drug resistant TB. There were 87,000 new cases of HIV-TB every year and deaths due to TB excluding HIV was 4, 23,000 whichis alarm for immediate effective action. The Indian government has resolved to eliminate TB by 2025.Consequently, Indian Council of Medical Research (ICMR) launched nation's first wide-scale trial for two newly invented vaccines of tuberculosis (TB) on 15/7/ 2019 to facilitate prevention in spread of Drug resistant TB (Mascarenhas, 2019). NDM-1(New-Delhi Metallo-beta - lactamase-1) is a gene produced by bacterial microorganisms which makes the concerned bacterium multi drug resistant. This gene produces an enzyme which makes the antibiotics resistant. This Gene has originated in India and was first detected in a Swedish patient who had visited India for a surgery in the year 2008. There after this resistant bacteria (Klebsiellapnemoniae) having MDR-1 gene had spread all over India and across 70 different countries all over the world. The Indian government had taken various measures to tackle this situation and also focused on improving sanitation and providing clean and healthy water. These measures in public health will definitely help in reducing microbial resistance (Aggarwal, 2019).

The Indian government had also taken strict action in August 2019 to combat the menace of MDR. Notable among them is the ban on colistin, one of the last resort

antibiotics for human infectious diseases. This ban is not only on use of colistin as a growth promoter but also on its manufacture, sale and distribution because the consumption of such food product whether meat or poultry would expose the Indian population on the risk of MDR (Ghafur, 2019).

Future Perspectives

Bacteriocins are already being used commercially for food preservation and as a probiotic but their use as a therapeutic agent against human diseases still in the development stage and a reason for much excitement in the scientific and medical community alike. A massive and sustained effort is required to achieve this goal to combat the threat of MDR in shortest possible period of time. Scientists from different parts of the world are trying to isolate a broad spectrum anti - pathogenic bacteriocin which could be as effective as antibiotic therapy and have a lot of untapped potential as therapeutic agents. A cocktail of bacteriocins with differing spectrum of action could be as effective as a broad spectrum antibiotic. Bacteriocins could be combined with an antibiotic without compromising on the efficacy but reducing the unwanted side effects of antibiotic therapy. This would also help prevent development of both antibiotic resistance and bacteriocin resistant microbes. The pairs or group of bacteriocins showing augmented bactericidal action when working together as compared to when they act alone is another property being looked for (Antonio et al., 2019). The future prospects for bacteriocins as therapeutic agents have lots of potential as shown promising activity against biofilms (Kim et al., 2019). Experts have estimated that by the year 2060 more than 20 new classes of antibiotics would be needed to cope-up with the challenge posed by antibiotic resistance (Li et al., 2018). Only A few antimicrobial peptides are approved so far by FDA and EMEA (Cattoir et al., 2019). The phama industry is reluctant to support research activities of bacteriocins due to high production cost. With commercialization of bacteriocin based products and improved low cost production techniques coupled with increase in demand with time it is estimated that the cost to the consumer will go down significantly.

CONCLUSION

The human population is heading towards disaster unless antibiotics with broader antimicrobial activity are developed soon. There may be a number of unpublished antibiotics which are in preclinical stage of development. Approval process for newly developed drugs that include bacteriocins and antimicrobial peptides by medical control councils has been slow due to several safety and clinical tests which involve analysis of resistance to antimicrobial activity, allergies and effect on immune system of hosts. Bacteriocins can be used for prevention of infections, to fight against antibiotic resistance and treatment owing to their diversity and abundance. Bacteriocins are an interesting option being studied for future use as a therapeutic option against multi drug resistant bacteria. Much more research is required towards development of novel effective bacteriocins which successfully target complex bacterial systems such as cell membranes.

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