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Probiotics: Current Trend in Combating Antimicrobial Resistance

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ABSTRACT

Probiotics are live bacteria, most commonly belonging to the *Lactobacillus* and *Bifidobacterium* genera, although strains of other species are also commercially available and beneficial to the host. From an antibiotic perspective, probiotics have been shown to reduce the risk of certain infections, such as certain types of gastro-intestinal, respiratory and other reproductive infections. This may be accompanied by a reduced need for antibiotics for secondary infections. Although antibiotics appear to be effective against most infections, resistance is increasing among bacteria. Probiotics are specifically selected to prevent cross-contamination or transmission of antibiotic resistance. It is recommended to use probiotics together with antibiotics to reduce incidence, duration and/or severity of antibiotic resistance. This provides better compatibility with antibiotics and thus reduces the development of resistance. The extent to which probiotics directly reduce the spread of antibiotics resistance has not yet been fully studied. However, maintaining the balance of the microbiome while using antibiotics has been the potential to reduce infection and consequently resistance. Probiotics may reduce the need for antibiotics thus the risk of infection.

Keywords: Probiotics, Antibiotic-resistant bacteria, Methicillin-resistant Staphylococcus aureus, Lactobacillus, Antimicrobial resistance

INTRODUCTION

Probiotics is a term derived from a Greek word meaning "for life" [1]. According to World Health Organization, probiotics was defined as "live microorganisms" which when administered in adequate doses confer a healthy benefit to the individual or host [2]. They must be administered in sufficient number to survive in the intestinal area or environment of the host and their effects must be a positive. Probiotics are present in the daily consumption of fermented milk including yoghurt and all other derivatives of milk. A large number of these organisms have been in use in research facilities, medical laboratories and in clinical facilities. Probiotics can either contain yeast or bacteria. They are available as capsules, powders, packets, tablets and syrups. A probiotic composition may involve a single microbe or several different microbes. Probiotics administration are always specific to a particular strain and it may not be applicable to another strain.

Antimicrobial resistance (AMR) occurs when microbes (bacteria, fungi, viruses) and parasites become able to adapt and thrive in the presence of antimicrobials that once inhibited their growths [3]. Antimicrobial resistance proves antibiotics ineffective to treat certain diseases and recently they have become resistant to the major therapies used against them. Infections caused from antimicrobial resistance causes severe illnesses and it also causes prolonged stay of individuals in hospitals increasing health care costs treatment failures, death of infected individual and leading to higher

medical costs [4]. A prime example of microbial resistance is *Staphylococcus aureus* to methicillin [3]. The rate of antimicrobial resistance is due to the overuse of antibiotics especially when they are used without proper prescriptions from a medical practitioner. The spread of AMR is propelled by the presence of antibiotics in population, contamination of fresh water, and pollution. For instance, in Europe, over nine billion euro has been invested to combat antimicrobial resistance per year [5]. Also, according to the Centers for Disease Control and Prevention (CDC), AMR adds to a 20 billion dollars surplus in direct healthcare cost in the United States, which is exclusive of about 35 billion dollars in loss of productivity annually.

Currently, in clinics and hospitals these antibiotic-resistant pathogens have caused numerous treatment failures leading to both high mortality and morbidity rate. Overall, the antibiotic resistance has prevailed and now have become a global health threat and menace that requires urgent attention from the health authorities worldwide [6]. In facing the problem on antibiotic resistance, the use of probiotics in place of antibiotics for the treatment of certain diseases of which some host organisms have been investigated [7]. Research have shown that instead of inhibiting pathogenic microbes through antibiotics, commensal and sometimes mutualistic microbes should be established in order to kill the growth of disease-causing microbes found in the same host microbial environment which is by the use of probiotics [6]. Furthermore, maintaining the "normal" microbiota in a host prevent health condition not of infectious etiology thus improving the general state of health.

The aim of this review is to explore the potential of probiotics to combat the increasing tide of antimicrobial resistance.

Mechanism of Action of Probiotics

Several probiotics has several mechanisms of actions and they all differ significantly in species and strains [8]. Their activity are not limited to the intestinal tract. They exert their adaptation on several immune cells including the cells involved in innate and adaptive immunity [9]. The major mechanism of probiotics includes: blockage of adhesion site, immunomodulation, effects on immune system, gut barrier function, epithelial adherence, probiotic antimicrobial factors, inhibitory substance production and anti-proliferative effect [10, 11].

In epithelial adherence, the intestinal lining remains attached to the intestine, of which constant change in the bacterial population with the existence of other microbes occurs. It's a major mechanism used in the maintenance of the intestinal lining and it protects the host from the environment. Defence mechanism used include antimicrobial peptides, epithelial junction adhesion complex, mucous layer and immunoglobulin A. disruption of the epithelial barrier can cause increased exposure of the intestine to several microbes causing an inflammatory response resulting to inflammatory bowel diseases [12, 13].

Bacteria present in probiotics compete with invading pathogens in the host. They compete for points of attachment on cells and the protective mucus layer. The competition between them is influenced by some characteristics of each of the probiotic strain. A prime example is the *S. boulardii* releases a substance that is sensitive to heat and this substance helps in the reduction of bacterial to the epithelial cells and reducing their adherence [13]. For barrier function enhancement, probiotics enhances the barrier function by modulating the cytoskeleton and tightening the junction for phosphorylation [10]. In the case of immunomodulation, probiotics helps in the control of the immune system and it does this in different ways [10]. When certain probiotics like *Lactobacillus acidophilus, Lactobacillus bulgaricus and Lactobacillus casei* are ingested they enhance the action of phagocytic cells and activate the production of macrophages [14]. The immune system comprises of the innate system and adaptive system. The host cells interact mostly with the intestinal epithelial cells and creating an interaction at the gut

barrier of the host. When probiotics microbes then migrate because they are mobile, they meet dendritic cells which are cells that aid in the initiation of all antigen specific immune responses. Their main function is to link the innate and adaptive immune system [15]. The dendritic cell and the intestinal epithelial cells both have Pattern Recognition receptors. Pattern recognition receptors capable of recognizing molecules commonly found in pathogens [16]. The interaction between the dendritic cell and the intestinal epithelial cell is important in the functioning of probiotics in the system and how it helps the overall healthy wellness of the host as shown in Figure 1.

Blockage of adhesion sites by probiotics aids in intestinal colonization and the modification of the immune system against pathogen attacks. Probiotics with pathogens to attach to intestinal epithelial cells causing a blockage. When probiotics are taken into the host body, they move to binding sites and block binding sites leaving limited spaces for pathogens to attach to the intestinal cells [10].

Inhibitory substance production by probiotics acts as an inhibitory substance by applying several effects against several microbes involved in food spoilage either gram positive or gram negative. In doing these probiotics produce substances like lactic and acetic bacteria, diacetyl, hydrogen peroxide, carbon dioxide and bacteriocins [17]. Bacteriocins are substances produced by lactic acid bacteria [18], it's a kind of ribosomal synthesized antimicrobial peptide that can cause the inhibition or death of bacterial strains that are closely related or unrelated. Bacteriocins are classified into two: gram negative bacteria (colicins and microcins) and gram-positive bacteria (Class I, II and III). The Class I example include: Nisin A, Nisin U, Nisin Z, Mersacidin, Labyrinthopeptin A2, and subtilosin A. The Class II example include: pediocin PA-1, lactococcin A, carnobacteriocin X, lactacin F, ABP-118, enterocin AS-48 and carnocyclin A. The Class III example include: Enterolisin A, Helveticin J and Caseicin 80 [19].

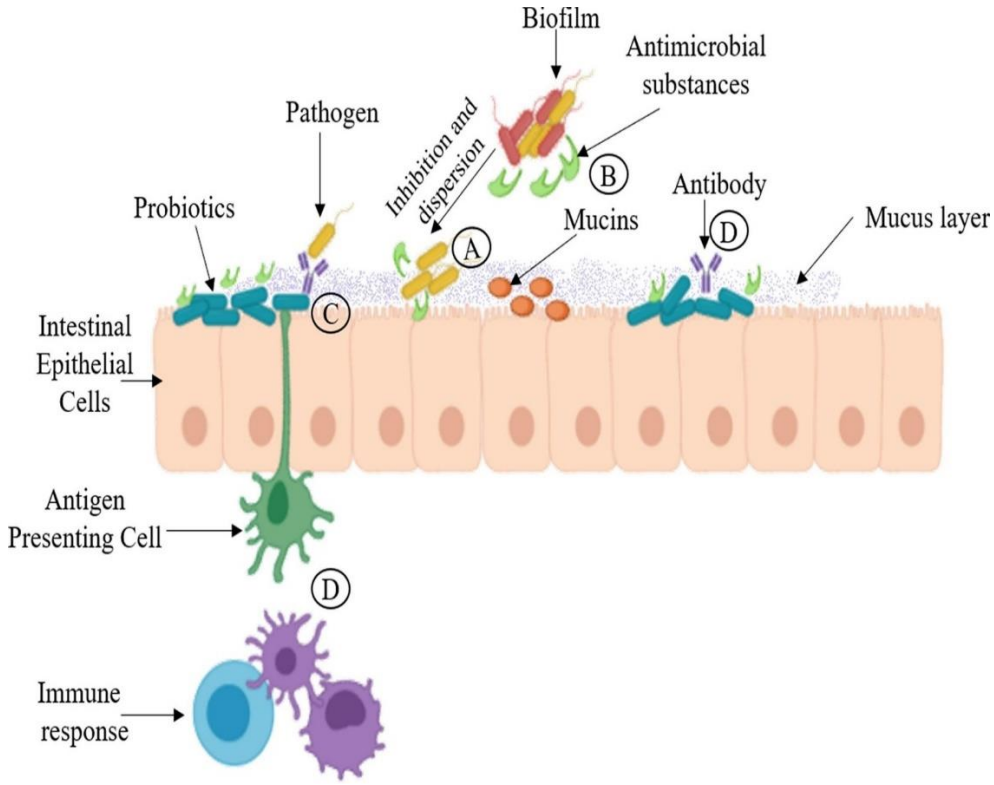

Figure 1: Mechanisms of action of probiotics. (A) Competitive exclusion of pathogenic microorganisms. (B) Production of antimicrobial substances. (C) Increased adhesion to the intestinal mucosa and improvement of the epithelial barrier. (D) Stimulation of the immune system [20]

Probiotics as alternatives to antibiotics

Currently, the world is facing a high rise of resistance in antibiotics. Due to the increasing number of antibiotic resistant strains, scientist and researchers are constantly in search for alternatives to solve this menace. Probiotics are been considered a good alternative to combat the global antimicrobial resistance threat. It is known that probiotics aid the microflora present in the gut, so the preparation of probiotics can prevent antibiotic associated diarrhoea (AAD). Asides AAD, there are documented studies with proven efficacy of probiotics in the mitigation of other intestinal disorders and gastrointestinal disorders like gastroenteritis, inflammatory bowel syndrome, *Helicobacter pylori* infection [21]. Certain probiotic strains: *Weissella confuse, Bacillus subtilis, Lactobacillus acidophilus, Lactobacillus casei*, and some other probiotic strains yet to be discovered has inhibitory effects against *H. pylori*. Salas-Jara et al [22] study on probiotics in the treatment of *H. pylori* infection. It was concluded that probiotics could serve as preventive measure against such infection via reduction of the pathogenic bacteria consequently eliminating inflammation in the stomach. The probiotics introduced serve as a protective shield.

Unlike like antibiotics, probiotics possess biofilms that aids their colonization in the guts. These biofilms also help them maintain their population. There are five different stages during biofilm formation which are the initial attachment, micro-colony formation, biofilm maturation and differentiation, biofilm detachment and dispersion [22, 23]. The increase in growth of probiotic bacteria suppresses and/or inhibit other pathogenic microbes present.

Probiotics are known to attach themselves to epithelial cells in the intestines thereby preventing further attachment of invading pathogens in the host. Moreover, are well known to elicit immune response. They also serve as a barrier to pathogenic microbes.

As an ideal alternative to antibiotics, probiotics can also improve the vaginal health. Bacterial vaginosis, a disruption that occurs in the vaginal microbiota [24]. When this occurs in the vagina there is a disruption in the microbiome because there is an increase in the microbial diversity in the vagina and also a high presence of anaerobic bacteria. Though there is a presence of an increased number of microbial diversity but there is also a reduction in the number of vagina microflora which is the *Lactobacillus* spp. The *Lactobacillus* present in the vagina use hydrogen peroxide as a means to checkmate the microbial population in the vagina. However, to treat these disease antibiotics need to be used. But recently, studies have shown that even after the use of antibiotics bacterial vaginosis can reoccur because generally antibiotics kills all microbes present in the body and when this happens there's still imbalance in the microbiota of the vagina. Therefore, causing an alteration of the *Lactobacilli* [25]. But when probiotics is introduced, it inhibits unwanted microbes thus, increasing the number of beneficial bacteria, and subsequently reducing the number of pathogenic microbes which pose as a threat to reproductive health [26 - 28].

Probiotics has been a good alternative for the treatment of Genitourinary Syndrome of Menopause (GSM). Genitourinary Syndrome of Menopause is a menopausal symptom and signs that happens when women get to their menopause age. It includes genital symptoms, sexual symptoms and urinary symptoms [29, 30]. It was previously called vulvovaginal atrophy or atrophic vaginitis. It is caused by a decrease in estrogen production in the body. In this symptom, there is a reduction in lactobacillus and an increase in anaerobic bacteria population which makes the vagina prone to cancer. The treatment of this symptom includes estrogen therapy and non estrogen therapy. In recent studies, it has been discovered that the combination of probiotics with estrogen can help to reduce symptoms that is associated with vulvovaginal atrophy. Generally, probiotics play a significant role in the reduction of reproductive organs

related issues, maintenance of the female reproductive tract health [31, 32] and enhancement of the vaginal local immunity [28].

Probiotics can beneficial in so many ways in the oral health of the host. It has also been suggested that the regular consumption of probiotics can also help in oral health issues. These dental issues include halitosis, gingivitis, periodontitis and cavities. When probiotic colonize the oral cavity they help in reducing the number of harmful pathogens and their properties. When a beneficial microbe is introduced to an area that is inflamed and infected, it can shift the environment from its harmful state to a more beneficial and favourable site and lessening its inflamed state [33]. The oral cavity is made up of the presence of soft and hard tissues. The soft tissues are like the oral mucosa while the hard tissues comprise of the teeth.

There are several variations present in the mouth and these variation present contributes to the diverse microbiota in the oral cavity. Some studies indicate that there is a possibility that consumption of products containing probiotics can help in the reduction of *Streptococci mutans* present in the saliva [34]. *Streptococcus mutans* is a gram-positive facultative anaerobe. It is one of the leading causes of the early stage of dental diseases in humans [35]. The probiotic species present are lactobacillus and bifidobacteria. Also, the intake of probiotics helps in the reduction of yeast cells of oral candida in humans. Oral candidiasis is an infection of the oral cavity *Candida albicans*. This diseas happens when the immune system of the host is compromised [36]. Beside the mentioned above, probiotics also does the following in oral health: Production of antimicrobial compounds including acids, Antagonisms against pathogenic organisms, Inhibition of adhesion and enhanced clearance, Decrease of MMP production (matrix metalloproteinase), Inhibit pathogen induced production of pro inflammatory cytokines.

Role of probiotics in combating antimicrobial resistance

Probiotics have many benefits and can control pathogenic bacteria. By reducing adhesion to cells, the production of organic acids antagonize pathogenic bacteria. Many probiotics produce antibacterial substances such as short chain fatty acids, hydrogen peroxide, nitric oxide, and bacteriocins that improve their ability to compete with other intestinal bacteria and most relevant pathogenic bacteria [37]. Moreover, the production of antibacterial agents is considered an important factor in the transformation of bacteria and effectiveness of probiotic bacteria [38], as the product of bacteriocin bacteria is important for the selection of probiotic bacteria.

Studies have shown that Lactobacillus strains play a positive role in protecting the host from urinary tract infections (UTI) [39]. For example, *Lactobacillus rhamnosus* GR1h has been reported to bind well to epithelial cells, especially in breast epithelial cells [40]. Furthermore, antagonists' activity of such bacteria may inhibit the binding of enteric and urinary tract bacterial pathogens [41].

The key challenge with the use of antibiotics is the constant emergence of resistance. It has been reported that lactic acid produced by Lactobacilli strains can increase the susceptibility of Gram-negative bacteria to antimicrobial agents [42].

In a retrospective study, the use of several strains of probiotics such as: *Saccharomyces cerevisiae, Corynebacterium accolens, Lactobacillus species, Streptomyces species, Enterococcus species* and *L. lactis* resulted in the reduction of biofilms. *Bacillus subtilis* and *Bacillus amyloliquefaciens*, have an inhibitory effect against biofilm-associated MRSA and methicillin-susceptible *S. aureus* (MSSA) [43].

Challenges in using probiotics for antimicrobial resistance

Currently, the world is running out of options to treat certain kinds of diseases. But some researchers and scientists suggest the medical world revert to the traditional

remedies available before the advent of antibiotics. Among all these traditional remedies, scientist chose probiotics [44]. It has created a major challenge for them. Scientists and doctors now face new challenges. They are working on developing modern types of foods, supplements, and treatments that meet safety standards and are convenient and beneficial. This is in line with European regulations. Additionally, there's a push to understand the genetic and molecular mechanisms of how probiotics work, ensuring optimal health benefits. The goal is to create targeted probiotic products that suit the specific needs of different groups of people, ensuring safety in their use.

CONCLUSION

According to the CDC, the threat level of antibiotic-resistant bacteria requires more monitoring and prevention activities. Serious threat such as methicillin-resistant *Staphylococcus aureus* (MRSA) have been combated using probiotics of *Bacillus spp*. However, there is need for further studies on other resistant threat such as: drug-resistant *Mycobacterium tuberculosis*, drug-resistant *Salmonella typhimurium*, multidrug-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Enterobacteriaceae* (CRE) and drug-resistant *Neisseria gonorrhoeae*.

Declaration by Authors

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