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Probiotics: Perspectives as Antimicrobial Therapy

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Abstract

Background: Growing upsurge in development of resistance to the existing antimicrobials, especially worsened by escalated overuse of antibiotics, has emerged as a huge challenge to the survival of mankind as well as livestock.

Aim and Objective: To assess the possibility of using probiotics as an alternative or complementary therapy to antibiotics in infectious diseases.

Design: A systematic review of the English medical literature concerning dynamics of probiotics as an antimicrobial therapy.

Salient findings: Nearly all available studies point to the antimicrobial activity of the probiotics with variations in the quantum of this property. Most studies confirm that probiotics used as a complementary therapy along with antibiotics are of value. As regards role of probiotics as alternatives to antibiotics, there is hardly any convincing evidence in the published literature favoring this. Furthermore, there is a need to establish the exact mechanism of action, optimal dose in different situations, duration of administration, etc.

Conclusion: In spite of the several benefits of probiotics in relation to the health of the gut, it remains debatable if the application of its formulations as an alternative to antibiotic therapy is acceptable. However, their role as a complementary therapy seems well recognized. Well-planned bio-guided studies, including clinical trials, are warranted to address the existing gaps and grey areas in the knowledge.

Clinical impact: Whereas use of probiotics as a complementary therapy with antibiotics may well be a useful approach, the same cannot be claimed in case of probiotics as an alternative to antimicrobials unless further studies bring about convincing evidence to this effect.

Keywords: Adjunct; Antibiotics; Antimicrobials; Antimicrobial resistance; Antimicrobial activity; Alternative antimicrobial therapy; Multidrug-resistance; Probiotics

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Introduction

All antimicrobials have the inherent ability to develop natural resistance, the so-called "Antimicrobial Resistance" (AMR), in due course of time [1]. The irrational and/or over use of antimicrobials is known to facilitate development of AMR earlier. Almost all available antimicrobials now fall in the AMR domain. Our last hopes (the so-called "last resort") too are moving in that direction. As a result, it is becoming very tough to treat serious infections, especially those caused by the Gram-negative pathogens. The situation is likely to take a critical turn if new antibiotics from new classes are not regularly developed in the years ahead. The consequences of that shall be in the form of proliferation of lethal bugs causing huge chunk of morbidity and mortality – a threat that mankind cannot afford to ignore [2]. In order to squeeze out of that precarious situation, scientists are working on the possible use of alternative therapies [3], such as antibodies, immunotherapy, bacteriophage or phage therapy, fecal biota transplant, antimicrobial peptides, probiotics, etc., as an alternative and/or a complementary therapy for antimicrobials.

This systematic review focuses on the studies on the use of probiotics as candidates for alternative antimicrobial therapy or as complementary therapy, discusses the implications of the documented evidence and points out future directions in the area.

Probiotics: An Overview

Probiotics are eco-friendly living microorganisms (bacteria, yeast), predominantly Gram-

Table 1: Major biologic functions of probiotics [4-6].

Improvement of microbial balance of the gut
Improvement of lactose tolerance
Prevention and control of diarrhea: Antibiotic-Associated Diarrhea (AAD), Cl. difficile-associated diarrhea, traveler's diarrhea, viral diarrhea of infancy)
Prevention of allergic diseases
Control of Inflammatory Bowel Diseases (IBD)
Prevention and control of constipation
Improvement of fertility in Polycystic Ovary Syndrome (PCOS)
Amelioration in stress and anxiety
Cancer prevention
Antimicrobial activity

positive bacteria, that mainly colonize the intestines of the Gastrointestinal Tract (GIT) and are beneficial to the host in so many ways. As microbial food supplements, when ingested in sufficient amounts, probiotics are capable of modulating biologic functions and causing stimulation of the immune system[4] with health benefits.

The most well-known probiotics are

A. Lactic acid bacteria species: *Lactococcus*, *Lactobacillus*, *Streptococcus*, *Enterococcus*), and

B. *Bifidobacterium*: *B. bifidum*, *B. infantis*, *B. lactis*

These microorganisms are able to withstand the destructive effects of the enzymes and acidity. Their contribution to host's health is via regulation of the GIT microbiome and biologic properties.

The major biologic functions of probiotics are listed in Table 1. Obviously, health benefits are predominantly gut-related. Somehow, these are the best studied ones too.

Probiotics exert their activity in various ways [4]. Table 2 presents different likely mechanisms of action of probiotics.

Multidrug-Resistance: Issues and Concerns

The popular acronym, "ESKAPE", refers to the group of Gram-positive and Gram-negative pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter*). These are the bacteria that are most frequently involved in AMR infections. These infections are a major health threat worldwide, more so in the resource-limited communities [5].

Emergence of Multidrug-Resistant (MDR) strains of Gram-negative bacteria in a big way in particular is a matter of grave concern. The Gram-negative bacteria (*Enterobacteriacea*, *Klebsiella pneumoniae*, *Pseudomonas aeuroginosa*, etc.) are known to be more resistant to antibiotics than Gram-positive bacteria (Methicillin-Resistant *Staphylococcus aureus*, Vancomycin-Resistant *Enterococcus faecium*, Drug-Resistant *Streptococcus pneumoniae*). The reasons include differences in the

- Cell wall,
- Efflux pumps, and
- Antimicrobial-destroying enzyme)

The development of resistance is a natural (intrinsic) phenomenon. Some factors, especially overuse of antibiotics, may cause acquired resistance. In a proportion of cases, AMR may well be both intrinsic and acquired.

Table 2: Probable mechanisms of action of probiotics.

Increased epithelial barrier
Increased adhesion to the intestinal mucosa
Inhibition of microbial adhesion
Competitive exclusion of pathogenic microorganisms
Production of antimicrobial substances
Immune system modulation

Since 1980s, as a consequence of increasing problem of resistance against the conventional antibiotics, clinicians are facing increasing problem of AMR. Now, they are left with limited options in pharmacotherapy of serious infections, especially the anaerobic and opportunistic ones in the Intensive Care Units (ICUs). In such infections, carbapenem was the antibiotic usually employed until the tail-end of 1990s.

The onset of 21st century was accompanied by massive spread of acquired carbapenem-resistance that had earlier been documented in 1990s as a result of production of the destructive enzyme, metallo-β-lactamase. The clinicians started employing colistin (polymyxin) – an agent that had remained cornered for a considerable time - tigecycline, fostomycin, aminoglycosides and quinolones as such or in combinations for carbapenem-resistant pathogens.

Subsequently, a significant occurrence came to limelight in the shape of the global spread of MDR 'superbug' gene. Coded as" blaNDM", it was first detected in New Delhi, India, in a Swedish patient of Indian origin. By now, the superbug has spread to over 100 countries across the globe, causing a massive setback to the above said antimicrobial therapies.

At present, cetazidime/avibactam, meropenem/vaborbactam and ceftolozane/tazobactam are being used to overcome the deadly MDR Gram-negative infections.

Undoubtedly, this strategy cannot sustain for a long time. At this difficult point of time, we are desperately in need of new antimicrobials, surely from classes other than the existing ones. If that does not happen in the forthcoming years, we may be left with no effective antimicrobials at our command to treat the serious MDR infections, especially when there is a tendency for emergence of XDR and PDR bugs.

Probiotics as Antimicrobials

Ever since the accidental discovery of the first antibiotic,

Table 3: Probiotics with antimicrobial activity [4].

Lactobacillus: *L. acidophilus*, *L. amylovorus*, *L. casei*, *L. crispatus*, *L. plantarum*, *L. casei Shirota*, *L. paracasei*, *L. rhamnosus*, *L. reuteri*, *L. johnssonii*, *L. helveticus* R0052, L. fermentum
Bifidobacterium: *B. bifidum*, B. infantis, B. lactis, B. adolescentis, B. animalis subsp. *Lactis*, B. longum R0175, *B. breve*
Remaining bacteria: *Saccharomyces bourlardii*, *Propionibacterium freudenreichii*, *Enterococcus faecalis*, *Enterococcus faecium*, *Lactococcus lactis*, *euconstoc mesenteroides*, *Pediococcus acidilacticiei*, *Sporolactobacillus* inulinus, *Escherichia coli*, *Saccharomyces cerevisiae var*. boulardi, Bacillus coagulans

penicillin, by the Nobel Laureate, Sir Alexander Fleming, in 1928 [8], infectious diseases continue to be usually treated with one or the other conventional antimicrobial agent. Unfortunately, though universally popular, this approach is handicapped by drug-specific Adverse Drug Reactions (ADRs). Furthermore, and more importantly, emergence of MDR pathogens those are capable of transferring themselves to XDR and even PDR pathogens.

Clearly, we need to search for alternatives in antimicrobial therapy with a particular focus on natural product-based therapies. Among various such potential therapies, probiotics have shown triggers as potentially anti-infective agents. However, only limited work has been done to study this aspect in an organized way.

About a decade back, Gupte and Patil [9] conducted a meta-analysis and highlighted on the evidence that probiotic strains could act as an adjunct to antibiotic therapy. This property is believed to be through improvement in antimicrobial activity, improved mucosal immunity and reduction in ADRs.

Over the recent years, some studies have evaluated role of probiotics as candidate antimicrobial agents. There is some evidence that probiotics may be effective in the treatment and prevention of infectious diseases [10-16]. Hence, the use of probiotics is being considered a promising strategy for the prevention and control of various infectious diseases.

In a study documented in 2019, Khmaladze et al. [17] have shown that the use of probiotics, *L. reunteri*, decreases the inflammatory process by virtue of antimicrobial activity against *S. aureus*, *S. pyogenes* and *Cutibacterium* as also anti-inflammatory and skin barrier enhancing functions.

More recent studies by Xu et al. cited by de Silva et al. [4] suggest that patients affected by COVID- 19 should use probiotics to avoid secondary infections on account of secondary intestinal microbial dysbiosis. According to the researchers, nutritional support along with application of probiotics regulates the balance of the intestinal microbiota, thereby cutting down the risk of secondary infection due to bacterial translocation.

According to a systematic review and meta-analysis by King et al. [18], probiotics, administered for lowering the risk of common acute infections in pediatric population, are associated with reduced antibiotic use. The authors recommend conduction of further well-designed studies for substantiating these findings in various population groups. The probiotics with antimicrobial activity are listed in Table 3.

Roadblocks in Application of Probiotics as Antimicrobial Therapy

Undoubtedly, there is enough convincing evidence favoring antimicrobial activity of probiotics. Yet, at present, there are genuine reservations on the use of probiotics as an alternative therapy for conventional antimicrobials. Why? The reasons include the following:

1. The quantum of antimicrobial activity of probiotics in various infections continues to be by and large unclear and needs further elucidation.

• Precise optimal doses and duration of administration of various probiotics remain ambiguous.

• Clinical efficacy of different probiotics is vague.

• Safety margin of different probiotics needs to be further evaluated. To ensure safety of the probiotics, it is important to exclude antimicrobial-resistant genes.

• Exact mechanism of action of different probiotics is yet to be established.

• Lack of standardization for clinical use of probiotics in various infectious diseases.

Obviously, in order to achieve optimal therapeutic benefit as alternatives to antimicrobials, further studies are warranted to tackle the aforesaid gray areas and gaps in knowledge.

Finally, it is felt that, though probiotics have an antimicrobial activity, at present there remain reservations against their use as an independent alternative to conventional antimicrobials. Nevertheless, it is surmised that probiotics may have a more acceptable role as a complementary/adjuvant therapy to conventional antimicrobial treatment.

Summary and Conclusions

Ever increasing crisis of AMR, worsened by the further hike in overuse of antimicrobials during the ongoing pandemic of COVID-19, has left hardly any room for complacency. Endeavors aimed at prevention and control of AMR through various mean (Gupte... control of) clearly need a big “push”. Among the strategies, various potential alternatives to antimicrobials are in the process of being explored.

As far as the probiotics are concerned, there is a considerable evidence favoring the several benefits of probiotics on the health of the gut as well as promising antimicrobial activity. Yet, it remains doubtful if the application of its formulations as an alternative to antibiotic therapy can be acceptable at present in the light of some well-meaning reservations. Well planned bio guided studies as well as clinical trials are warranted to address the existing gaps and grey areas in the available knowledge with special reference to their use as an alternative to antibiotics. However, their role as a complementary or adjuvant therapy seems fairly in place.

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