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EC PHARMACOLOGY AND TOXICOLOGY
Short Communication

Probiotics and Immunity: Exploring the Development of Probiotics Concept

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Received: September 24, 2024; **Published:** October 09, 2024

Abstract

The human gut is the home of billions of microorganisms repressing more than thousands of species. Cumulatively, these microorganisms make a microenvironment in the gut and thus influence many of the host's functions. Among them, a beneficial class of microorganisms are known as probiotics, which are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host. Probiotics have selection criteria and possess vast applications ranging from technological functions to disease treatment. The human gut epithelial lining represents a major part that contains more immune cells than any other part. Probiotics have the property of attachment to the intestinal epithelial cells (IECs), and through this attachment they perform their action. Likewise, the probiotics in IECs also activate the pro-inflammatory responses either by the activation of cytokines or the production of lipopolysaccharide and thus help in the prevention and treatment of different diseases.

Keywords: *Probiotics; Inflammation; Immunity; Gut Microbiota*

Aims of the Study

This article aimed to shed light on the basics of probiotic development and answer how the probiotic concept was developed. It also briefly explains the various aspects of probiotics.

Introduction

Microorganisms are found in all environmental habitats, with varying species and numbers. It is estimated that around 159,000 species of microorganisms have existed for 3.5. billion years in all these environments [1,2]. These microorganisms have a potential impact on all forms of life, both in positive and negative ways. Their potential role in biotechnological, food, and pharmaceutical industries showcases their positive face, while disease-causing potential, disease transmission, and food spoilage highlight their threats to animals and humans [3]. Over the period, the role of microorganisms in climate change and their impacts on the environments has been identified [4-6]. Particularly in humans, both positive and negative aspects of microbes are found, indicating to use them in positive applications or identify potential ways to get rid of them [7,8]. This dual nature of microorganisms highlights that they can do more if recognized in a proper way. Thus, researchers took interest and explored their multiple applications in animals and human immunology, biotechnology, and microbiology.

Microbiota: Microbiota is a cumulative term that describes the overall microbial composition of that particular area. For instance, the skin microbiota and gut microbiota in humans represent the overall microenvironment of the skin and gut, respectively [7-10]. The human gut is the home of billions of microorganisms, which represent more than thousands of bacterial species. Cumulatively, these

microorganisms make a microenvironment in the gut and thus influence many of the host's functions [11,12]. Likewise, the intestinal microbiota also gives a genome burden of 600,000 to 3.3 million genes [13,14]. Among them, a beneficial class of microorganisms are known as probiotics, which are considered the friendly microbes of the host. In the early 20th century, scientists already recognized the role of fermented foods and their impact on human activity.

The Elie Metchnikoff idea: Elie Metchnikoff (a cellular immunologist) was the man behind the concept of longevity and proposed that if we change the gut microflora with the beneficial microbes (now called probiotics), it will promote longevity [15]. He also took interest in the cellular immunological mechanism through which these microorganisms perform their functions. Although he doesn't use the term probiotics for these bacteria instead calls them friendly and good bacteria. Elie was in search to identify the actual reason for the longevity and to identify why the consumption of fermented yogurt by people in hilly areas gives healthy benefits. He formulated his idea and stated that consumptions of *Lactobacillus* in the fermentation reduce the toxicity of the indigenous microflora and exert a beneficial influence on health [12,15-17]. He also formulated that human ailments are causes due to the putrefaction of intestinal microflora and thus attract the researchers to explore them in detail [18]. The major developments that occur in the course of probiotic development are summarized in figure 1.

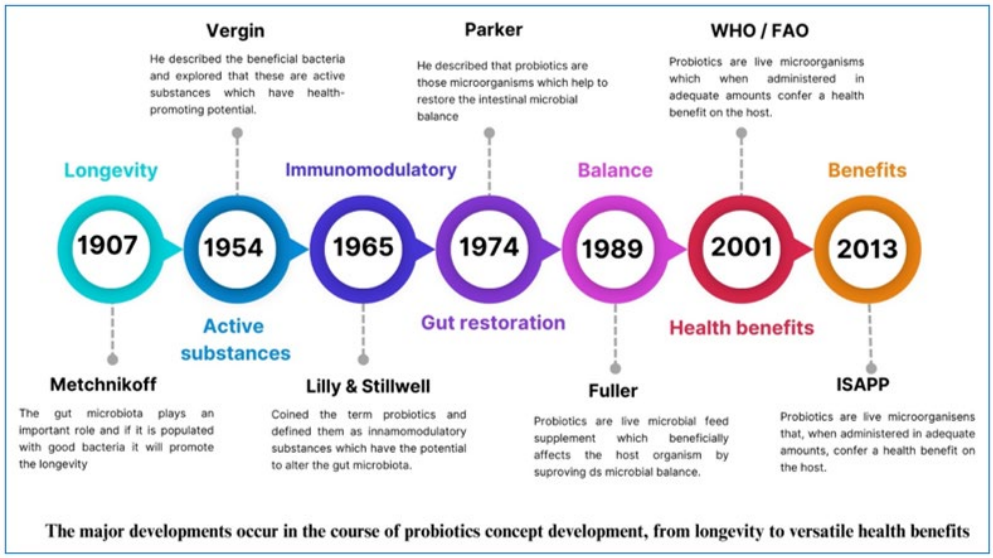

Figure 1: *The major developments occur in the course of probiotics concept development, from longevity to versatile health benefits.*

Development in probiotics: Following the concept of longevity, many scientists are trying to explore different microorganisms for their beneficial role. Different aspects were touched and tried to develop and identify more beneficial and new potential areas in this field. In the 1950s, Vergin described this concept for those substances that give health benefits. Following in the mid-1960s, Lilly and Stillwell formally coined the term probiotics and defined them as any substance that has immunomodulatory potential and can change the host's immunity [16,19]. Over the time, different changes were made in all aspects of probiotics, like the proposed selection criteria, identifying different microorganisms, elucidating their mechanisms of action, exploring their health benefits, putting forward their commercialization guidelines, and identifying them as a game changer in other aspects. Thus, in the beginning of 21st century, the World Health Organization and Food and Agriculture Organization defined probiotics as "live microorganisms which when administered in adequate amounts confer

a health benefit on the host". After the WHO definition, the probiotic field had exceptional attraction, and it was explored in many areas. In 2013, the International Scientific Association for Probiotics and Prebiotics (ISAPP) update the WHO definition and defined them as "live microorganisms that, when administered in adequate amounts, confer a benefit to the host". The ISAPP definition is the current recognized definition of probiotics [20-23].

Probiotics microorganisms: Development in the probiotics is recognized by the number of publications dedicated to it. Recently, thousands of papers have been solely dedicated to the different aspects of probiotics, which clearly reflect their potentials and impacts. Seven groups of microorganisms are currently proposed to have the probiotic species dominated by *Lactobacillus* and *Bifidobacterium*, followed by enterococcal species. The former two got the status of Generally Recognized As Safe (GRAS) and Qualified Presumptions of Safety (QPS), while the third (*Enterococcus*) is still not included in these lists. Though there are many commercial probiotics available that have enterococcal origin [16,23,24].

Selection criteria: These microorganisms are selected while following the proposed selection criteria, which include safe nature, tolerance to harsh conditions, survival ability in the gut, production of antibacterial substances, and the potential to kill and eradicate the pathogens. Besides other criteria, adherence to the intestinal mucosal and epithelial cells is of great importance, as this adherence is directly related to the probiotics survivability, pathogen killing, and immunomodulatory actions [19,25,26].

Mechanism of action: The mechanism of probiotic action is still not clear. Different mechanisms are proposed, which are mostly based on their epithelial cell attachment, survivability and viability in the gut, and their effectiveness in harsh conditions. Their effect on the host immune system is the area of interest since the field originated [16]. The human's immune system provides protection to the body through the secretion or production of different substances. These immune cells and molecules are present in different parts of the body with different percentages and perform their function continuously. Any foreign molecule called antigen, when come into contact, these cells are activated and killed by different means. Both innate and adoptive immunity perform its functions and contribute to the overall health [27]. The presence of microorganisms in the body, particularly in the gut and intestine, produces a complex and intricate microenvironment. Their interaction with the immune system can lead to different functions, which also include the protection of the body against different diseases.

Gut dysbiosis: Generally, in the gut there is eubiosis status, representing the balance distribution of billions of microorganisms. These microorganisms communicate with each other following a phenomenon called quorum sensing, which is facilitated by the production of small peptides called auto-inducers. This bacterial communication performs various functions and contributes to the normal gut flora [28]. Any disturbance in this intricate balance produces gut dysbiosis and hence leads to affect its associated functions. Different metabolic and digestive disorders like obesity, diabetes, etc. are associated with this dysbiosis [13]. The intestinal layers provide a practical barrier for the lumen and the intestine. This lining is populated with both immune cells and bacterial cells, which are in intricate balance with each other [27].

Immune system and probiotics: As described, the probiotics in the gut, better known for their gut-restoration potential, can help to overcome this misbalance and recreate the eubiosis status in the gut [16]. In case of any foreign molecules that cause the disturbance of the gut, the probiotics can perform their functions and restore the normal physiology of the gut. The direct association of probiotics with host immunity relies on the interaction of pattern recognition receptors (PRR) with microbe-associated molecular patterns (MAMPs) on the host intestinal mucosal cells [16]. This interaction can lead to upregulate the synthesis of tight junction proteins, which trigger the activation of PRP in the intestinal lining [16]. The mucosal functioning is also affected by the downregulation potential of probiotics over the production of pro-inflammatory cytokines like IL-12, TNF-a, and IFN-c [16,27,29]. Part of the gut microbiota can also affect the immune system by controlling the Treg maturation or by driving IL-10 production [27,30-32]. The general effect of probiotics on immunity is reflected in figure 2.

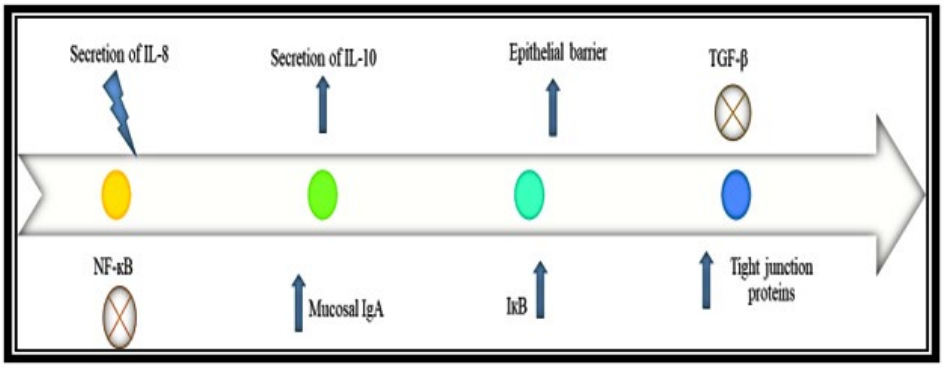

Figure 2: *The general mechanism of action of probiotics on immunity. The secretion of interleukin 8 (IL-8) is decreased while IL-10 is increased. The epithelial functions, mucosal IgA level, and tight junction proteins are enhanced. IκB (inhibitor of NF-κB) level is improved while NF-κB (nuclear factor κB) and Transforming growth factor beta (TGF-β) are lowered.*

Probiotics help in immune diseases: There is a growing awareness about the interaction of probiotics with the immune system. A study showed that probiotic exposure protects against inflammatory bowel diseases (IBD) by stimulating the immune system [18]. Likewise, the *lactobacillus* administration was found to reduce the atopic eczema by 50%. The role of probiotics becomes more prone when there is dysbiosis and the concentration of pathogenic bacteria exceeds that of beneficial bacteria [18]. Besides the IBD treatment, there are many other inflammatory diseases that are treated with probiotics while following the immunomodulatory effects.

Discussion

Critical analysis of the current literature clearly indicates the role of probiotics in immunity modulation, either upregulation or downregulation facilitated by different helper cells and molecules. This intricate regulation and interaction (microbe-immune interaction) can lead to the production of other regulatory and stimulatory molecules, which in turn trigger many important functions, including the treatment of inflammatory diseases. Recently, the role of the gut microbiota is well recognized for the host psychological functions. The bidirectional communication of gut and brain explores many areas of research and adds more value to the gut microbiota, particularly the good bacteria, i.e. probiotics.

Summary

In summary, the use of fermented substances and food in the ancient populations attracted the Elie attention to explore the mechanistic way of their health benefit. The Elie research gives the idea of longevity of life by repopulating the gut microflora with beneficial bacteria if dysbiosis happens. Moreover, the role of the immune system is better recognized for its interaction with the intestinal bacteria (probiotics) and thus gives a route of its actions. The effect of probiotics on the immune system is thus the main player in the longevity of life, and hence the Elie concept was not only recognized but got exceptional exposure in the scientific community.

Conflict of Interest

The authors have no conflict of interest.

Acknowledgments

This research project was financially supported by the "Seed Fund" from ICCBS, University of Karachi, and Higher Education Commission of Pakistan (NRPU: 20-151/Acad-R/03; 20–1339/R&D/09) to Syed Abid Ali.

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Volume 12 Issue 10 October 2024