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Role of probiotic bacteria against virus pathogenesis: Insight of immunological stimulations and possible defence against covid-19

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Abstract

Probiotics have appeared a beneficial effects on human wellbeing, the immunomodulatory activities is the most critical mechanism of probiotics, researchers commenced assessing the impact of some immunobiotics, on pathogenic microorganisms as well as on viruses. The novel coronavirus disease (COVID-19) is pandemic in 2019 and 2020, which is having a massive world influence on human health and so economic disruption. Researchers do their best efforts to discover new drugs or vaccines against COVID-19 and try to use natural products to treat the virus. Numerous works have endorsed the possible antiviral activity of some probiotics. The extreme use of antibiotecs, which is reliable for many antagonistic impact leading us to make more studies on natural agents, probiotics are selected as the best substitutes to these antiviral agents and they act as natural immune sauces, which produce the viral disease fighting. This review deliberates the profits of probiotics, their role in immune power boost towards viral disorders, and insight into the role of probiotics against COVID-19.

Keywords: COVID-19; Immunological stimulation; Probiotics; Virus.

Introduction

The concept of probiotics evolved gradually, but significant changes occurred during the 70s and 80s, primarily driven by the rapid advancements and applicability of molecular biological techniques [1]. A modern definition of probiotics was articulated by Fuller [2], characterizing them as live microbial feed additions that beneficially influence humans by promoting microbial balance in the Gastric Intestinal Tract (GIT). This includes the prevention of pathogenic microorganisms in fermented foods, addressing undesirable odors, tastes, and textures. Conditions such as pH reduction or the production of antibacterial peptides like bacteriocins create a favorable environment for probiotics, giving them an edge over other microorganisms [3]. Several studies have not only observed the effects of probiotics on Immunoglobulin (Ig) production and secretion but also examined their influence on the quantity and activity of immune cells [25]. For instance, elderly subjects consuming a milk product containing Bifidobacterium lactis (B. lactis HN019) experienced

increased activity of phagocytes and Natural Killer (NK) cells, similar to TC cells. Concurrently, there was an observed rise in the number of NK cells and T cells during probiotic consumption. Didierlaurent et al. [26] delved into the mechanisms of the immune response of the intestinal microbiota, focusing on the direction of interleukins, tumor necrosis factor, and interleukins creation in macrophages. Interleukins play a vital role in establishing balanced levels of T-helper 1 and 2 (Th1,2) responses, contributing significantly to the defense against intracellular microorganisms. Miles [27] conducted extensive research over several decades, demonstrating the substantial impact of the endogenous microbiota on the activity and development of the immune system. Germ-free mice studies highlighted the importance of the microbiota, as the absence of microbes not only affected immune function but also led to increased food consumption and a reduction in the development of certain organs. Furthermore, studies have explored the health-promoting effects of Exopolysaccharides (EPSs) from probiotic microorganisms, including anti-tumor activity and cholera toxin neutralization [9]. For instance, B-glucan extracted from Pediococcus parvulus exhibited antibacterial, antioxidant, and anticancer activities [10,11]. Lactobacillus acidophilus and its exopolysaccharides displayed anticancer activities in vivo and in vitro against Ehrlich Ascites Carcinoma (EAC) cells [12,13].

The primary mechanism for microbial competition and the elimination of pathogens involves lowering the pH in the immediate area around probiotic cells, creating an unfavorable environment for many pathogenic bacteria. Additionally, probiotics produce a range of antimicrobial compounds and metabolites, actively contributing to the creation of a hostile environment [14]. To be considered a probiotic, microorganisms must survive passage through the gastrointestinal tract, encountering gastric juice, bile, and pancreatic juice while offering health-strengthening benefits such as immune stimulation, diarrhea prevention, and pathogen inhibition [6]. Food preservation with probiotic cultures may also control the growth of pathogenic and/or spoilage microorganisms in fermented foods [15]. In the small intestine, the number of microbes increases due to more favorable conditions, supporting microbial life compared to the very low pH levels in other parts of the gastrointestinal tract. However, the duodenum and jejunum, optimized for nutrient absorption, leave limited or no food for microbes to feed on [17]. The primary target of ingested probiotics in the intestine is the small intestine, where their therapeutic activity stems from competition with pathogens for nutrients and mucosal adherence, the release of antimicrobial compounds, and the modulation of mucosal immune responses [18]. Prebiotics and synbiotics share a similar goal of promoting the growth of "healthy" bacteria in the digestive tract after ingestion [19]. Research has extensively explored the composition and quantity of microbes in the gastrointestinal tract, establishing mechanisms utilized by the GIT microbiota and probiotics [20]. These mechanisms, contributing to the symbiosis between the human host and the microbiota, can be broadly categorized into physical or biochemical modes of action. Physical mechanisms include intestinal adhesion and microbial competition, while biochemical mechanisms comprise epithelial barrier enhancement, anti-microbial compound production and secretion, and immunological stimulation and modification. Probiotics, differentiating between bacterial intercommunication and host-bacteria interaction, secrete various components, such as antimicrobial compounds and metabolites, modifying redox potential, and O_2 consumption, all contributing to an overall strategy of pathogenic exclusion [22].

Probiotics stimulate the immunological system

Continuing, a Japanese study revealed an elevation in Immunoglobulin A (IgA) levels following the consumption of the probiotic strain B. lactis Bb-12 after polio vaccination in children aged 15-31 months [23]. Similarly, Nicaise et al. reported comparable results in a study involving small children (average age 16 months) who were administered a Lactobacillus strain during rotavirus infection. Substantial increases in IgG, IgA, and IgM were observed in children receiving the probiotic strain [24]. Probiotics' impact on the production and secretion of immunoglobulins is not the only aspect under scrutiny; various studies have also delved into the influence of probiotics on the quantity and activity of immune cells [25]. An example includes elderly subjects who consumed a milk product containing Bifidobacterium lactis (B. lactis HN019), resulting in a significant enhancement in the activity of phagocytes and Natural Killer (NK) cells, akin to TC cells. Moreover, an increase in the number of NK cells and T cells was noted during the consumption of the probiotic bacteria. Didierlaurent et al. elucidated the mechanism (s) of the immune response of the intestinal microbiota by observing the production of interleukins, tumor necrosis factor, and interleukins in macrophages. Interleukins play a crucial role in establishing balanced levels of T-helper 1 and 2 (Th1,2) responses and are pivotal in the defense against intracellular microorganisms. Miles [27] extensively investigated this mechanism, spanning several decades, wherein it became widely accepted that the endogenous microbiota significantly influences the activity and development of our immune system. The importance of the microbiota's role has been underscored in studies involving germ-free mice, as highlighted by Smith [28]. It was observed that not only did the absence of microbes affect immune function in germ-free mice, but it also led to increased food consumption and a reduction in the development of certain organs.

Viral pathogenesis: Viral diseases encompass the combined effects of infection replication and the immune response within the host. The interest in viral pathogenesis stems from the desire to treat or eliminate viral infections affecting humans. Research endeavors aim to identify the viral and host genes influencing disease. For a virus to infect its host, it must first infiltrate cells at the body's surfaces, such as the mucosal linings of external organs like the respiratory, alimentary, and urogenital tracts, as well as the outer surface of the eye (conjunctival membranes or cornea). Successful infection in the host requires three conditions to be met: 1) Adequate virus availability to initiate infection, 2) Accessibility and receptivity of cells at the infection site, and 3) Initial absence or ineffectiveness of indigenous host antiviral defense systems [29]. The pathogenesis of viral diseases results from the production of toxins (acting intracellularly, systemically, or both), depletion of nutrients, obstruction of vital tissues, or triggering hypersensitivity or auto-allergic reactions [30]. The pathogenicity of viruses is not solely determined by the biochemical ability to replicate in host organs; strains of viruses replicate in host cells and exhibit diverse behaviors due to

varied capacities to counteract host defense mechanisms and induce tissue damage [31]. Most viral infections are subclinical, indicating that the body's immune system can thwart viruses and prevent disease manifestation before symptoms become apparent. These asymptomatic infections hold significant epidemiological importance as they contribute to the widespread dissemination of the virus across the population and confer immunity [32]. Various factors influence disease mechanisms, with the initial factor being the quantity of virus available to organs and tissues. Accessibility is influenced by physical barriers like mucus and tissue barriers, as well as natural defense mechanisms. If cells support viral replication, the virus proliferates within organs and tissues [33]. Viral disease occurs only when the virus replicates sufficiently to directly damage cells, release toxic compounds from infected tissues, or impair organ function due to the host immune response reacting to the presence of viral antigens [34].

Antiviral activities of probiotics

Probiotic bacteria have garnered significant attention from researchers as a pivotal tool for modulating the microbiota and maintaining health status. Numerous mechanisms contribute to the beneficial impact of probiotics, including the production of antibacterial, antifungal, and antiviral compounds, as well as the regulation of immune responses, inflammation, stimulation of mucus discharge, and maturation of dendritic cells [35]. Probiotic strains such as Lactobacillus and Bifidobacterium have been investigated for their inhibitory and regulatory effects on viral infections, demonstrating effectiveness against antirotavirus diseases Lehtoranta, [36]. Additionally, these probiotic bacteria offer multiple potential health benefits, such as inhibiting gastroenteric pathogens, enhancing immune responses, and neutralizing viruses [37].

Orally administered probiotic strains have been shown to promote respiratory immunity and resistance to viral respiratory tract diseases. For instance, oral intake of Lactobacillus bacteria has been associated with reduced signs of influenza infection, lower virus titers in the lungs or nasal washings of infected mice, increased body weight, and improved survival during infection [38]. The innate immune response and cellular proliferation of epithelial cells are also promoted by orally administered probiotics like L. casei, Bifidobacterium bifidum, Lactobacillus rhamnosus, and Streptococcus thermophiles. Several studies have demonstrated the efficacy of probiotics in the treatment of rotavirus [40]. The mechanisms of action of probiotics against viruses are illustrated in Figure 1.

Probiotics as anti-respiratory virus infections

Respiratory viral infections rank as the most prevalent diseases in humans, contributing significantly to morbidity and mortality worldwide. With over 200 types of respiratory viruses affecting humans, the predominant culprits include Human Rhinoviruses (HRV) and Human Enteroviruses (HEV) [41]. Influenza viruses, Respiratory Syncytial Virus (RSV), adenoviruses, coronaviruses, and parainfluenza viruses collectively contribute to a broad spectrum of respiratory diseases [42]. Numerous studies have highlighted the positive effects of probiotic bacteria on respiratory virus diseases in humans. For instance, L. rhamnosus GG has been shown to reduce the risk of Respiratory Tract Infections (RTIs) and the duration of RTI episodes [43]. Additionally, L. casei rhamnosusin has been found to decrease the frequency of RTIs [44]. Probiotic bacteria, such as Bifidobacteria and Lactobacilli, have demonstrated efficacy in reducing influenza virus presence in the respiratory tract [45,46]. In infants, the combination of L. fermentum CECT5716 with prebiotics has been associated with a lower incidence of upper and lower RTIs [47]. Adults taking L. fermentum after influenza virus vaccination experienced a decrease in the number of RTIs and an improvement in antigen-specific IgA formation [48]. Consortiums of various probiotic bacteria types have also proven effective in mitigating the risk of RTIs. For example, a consortium of L. rhamnosus Lc 705, L. rhamnosus GG, B. breve Bb 99, and P. freudenreichii sp. reduced the incidence of otitis in prone children. Another consortium of L. rhamnosus GG and B. animalis ssp. decreased the occurrence of recurrent RTIs, while a consortium of L. acidophilus and B. bifidum in healthy children diminished the duration of acute RTI symptoms [49,50]. Furthermore, a consortium of L. rhamnosus, L. rhamnosus, B. breve, and P. freudenreichii demonstrated a reduction in human bocavirus presence in the nasopharynx [39]. Lin et al. [44] reported reduced odds of viral infection in healthy children who consumed L. casei rhamnosus. A consortium of L. gasseri, B. longum, and B. bifidum decreased the duration of RTI symptoms, and a combination of L. rhamnosus GG and B. animalis ssp. lactis Bb12 consortium reduced both the duration and severity of upper RTI symptoms [49,51]. While the exact anti-Respiratory Tract Infection (RTI) mechanisms of probiotics remain unclear, Lehtoranta et al. [36] proposed that probiotics may impede the adsorption and cell entry of the virus. Additionally, probiotics may produce metabolites and compounds with direct antiviral effects. Ultimately, probiotics might contribute to immunomodulation with cells, initiating antiviral protection.

Probiotic prevent infections and relevance to covid-19

A comprehensive study has extensively documented the effects of probiotic strains against common respiratory viruses, drawing evidence from both clinical and experimental research [52,53]. However, none of these investigations have specifically explored the impact of probiotics on the novel SARS-CoV-2 infection. This should not dismiss or negate this approach, especially considering that the effects of probiotics against various Covid strains have been investigated [45]. The "China's National Health Commission and National Administration of Traditional Chinese Medicine" have recommended the use of probiotics in treating patients with severe COVID-19 infection. The objective is to maintain microbial balance and prevent secondary bacterial infections [55]. Senapati et al. [56] suggested that bioengineered probiotics carrying cell surface-bound or secretory human Angiotensin-Converting Enzyme (ACE2) could be a valuable pharmacological tool to resist SARS-CoV-2 infection. Lactobacillus paracasei expressing secretory human ACE2 is considered a live vector for orally delivering human ACE2 [57]. Probiotic bacteria, such as Lactobacilli and Bifidobacteria, have demonstrated a favorable impact in suppressing gut dysbiosis triggered by SARS-CoV-2 infection [58]. The metabolic products of Lactobacillus plantarum have been identified as potential antiviral agents, computationally proven to hinder COVID-19 at various levels. This suggests the possibility of treatment using plantaricin metabolites until a highly specific antiviral drug for COVID-19 is discovered [59]. Studies by Morrow et al. [50] and Zeng et al. [61] reported that patients on mechanical ventilation provided with probiotics like "Lactobacillus rhamnosus GG, live Bacillus subtilis, and Enterococcus faecalis" experienced significantly fewer ventilator-associated pneumonia cases compared to those given a placebo. However, the effectiveness of probiotic strains in reducing severe care unit mortality and inpatient mortality remains uncertain. Fanos et al. [62] emphasized the

Figure 1: Probiotics may prevent viral infections through several mechanisms.

potential of probiotic bacteria, particularly bifidobacteria and lactobacilli, in supporting recovery from various aspects of COVID-19, including nutritional, antiviral, anti-coronavirus, and miscellaneous interventions. Probiotics play a significant role in the immune system, impacting alveolar macrophages, neutrophils, natural killer cells, and amplifying levels of pro-inflammatory cytokines in the lungs [63,64]. The production of plantaricin, lactic acid, acetic acid, and gamma-aminobutyric by probiotic bacteria contributes to antiviral immunity [65].

Lin et al. [66] investigated the vital role of the immune system in healing severe acute respiratory coronavirus through modifications in peripheral blood T lymphocyte subsections, offering insights into infection diagnosis and treatment. Therefore, a targeted approach to altering gut microbiota may be crucial as a therapeutic advancement for COVID-19 and its comorbidities [58]. In addition, probiotics, vitamin consortium supplementation, and balanced diets could aid in supporting the immune system during the COVID-19 epidemic [67].

Probiotics as anti-Human Papillomavirus (HPV)

Human PapillomaViruses (HPV) stand out as the predominant sexually transmitted infections in the public domain. HPV infection is a fundamental contributor to cervical cancer [68]. Probiotics play a role in facilitating the resolution of HPV-related cytological abnormalities [69]. Demonstrated efficacy includes the reduction of vaginal colonization by pathogenic microorganisms [70]. Probiotic bacteria contribute to the restoration and maintenance of normal vaginal microflora, proving beneficial in the treatment and prevention of Bacterial Vaginosis (BV) and vulvovaginal candidiasis [71,72]. Lactobacillus casei has shown efficacy in promoting HPV clearance [69]. Li et al. [73] reported that vaginal probiotic use decreases the rate of HPV infection and hinders the clearance of HPV infection. Cassano et al. [74] observed a positive effect when supplementing conventional therapy with probiotics for cutaneous warts, also caused by HPVs. Verhoeven et al. [69] demonstrated the impact of probiotics on mucosal HPV and its consequences. Probiotic interventions have the potential to reduce productive viral infections, inducing a clinically "latent" HPV stage [75]. Ou et al. [70] found that Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC- did not influence genital high-risk HPV permission but may have reduced rates of slightly abnormal and abnormal cervical smears. The presence of a higher number of probiotic strains in the vagina may hinder HPV infections or their progression by promoting innate and adaptive immunity, the primary defense against viral infections [70]. Probiotic strains have the ability to deactivate viruses [76]. Palma et al. [77] revealed that HPV clearance was more pronounced with the treatment of metronidazole combined with 6 months of vaginal Lactobacillus application compared to a 3-month application. Reid [78] proposed that the mechanism underlying the use of probiotic strains in HPV clearance involves the creation of a synergistic environment, wherein the antiviral effects of probiotic bacteria result from the production of compounds such as biosurfactants, H_2O_2, lactic acid, bacteriocins, and co-aggregation molecules.

Herpes Simplex Virus type 2 (HSV-2)

Herpes Simplex Virus type 2 (HSV-2) is the most prevalent viral sexually transmitted disease. The vagina harbors over twenty species of lactobacilli, with Lactobacillus crispatus being the predominant colonizer in the healthy female vagina [79,80]. According to Mousavi et al. [81], Lactobacillus crispatus plays a preventive role by trapping HSV-2 particles, and microcolonies of L. crispatus obstruct HSV-2 receptors, impeding viral entry during the initial infection stages. Pre-treatment with Lactobacillus gasseri strain on Vero cells, as reported by Zabihollahi et al. [82] and Al Kassaa et al. [83], significantly inhibits the infectivity of both HSV-1 and HSV-2. Khani et al. [84] found that Lactobacillus rhamnosus enhances macrophage viability, exhibiting more efficient exclusion and activation against HSV-1 compared to non-probiotic Escherichia coli. Administration of 1×10^9 cfu/mL of lactic acid bacteria resulted in a reduction of complications caused by genital herpes due to HSV-2 [95]. Additionally, supernatants of Lactobacillus sp. and Enterococcus sp. inhibited HSV-1 viral replication [85]. Goudarzi and Fazeli [86] demonstrated that L. acidophilus can influence HSV-2 without producing H_2O_2 or H+ ions or acidifying the environment. While various lactobacillus species exhibit inhibitory effects against HSV, the precise mechanism of action in countering HSV infection remains unclear [38]. Deplancke et al. [87] proposed that lactobacilli may prevent viral reproduction by hindering attachment to cell receptors or by stimulating epithelial cells to pro-

duce antimicrobial compounds.

Probiotics are used as treatments for acute rotavirus diarrhea

Rotavirus stands as a significant contributor to severe gastroenteritis in infants and young children, manifesting in a spectrum of clinical symptoms such as profound diarrhea, vomiting leading to fatal dehydration, shock, and even death. Although the symptoms typically resolve within 3-7 days, they may persist for up to 2-3 weeks. The implementation of vaccine programs is contingent on cost considerations. Therefore, it is crucial to explore new preventive or therapeutic agents to counteract the infectious disease caused by rotavirus. An alternative approach involving antiviral agents suggests the utilization of probiotic organisms [88]. Rotavirus, the leading cause of diarrhea in infants under one year of age in developing countries, results in approximately 600,000 deaths annually. Many studies are exploring the use of natural products to address rotavirus infections. Grandy et al. [90] observed a reduction in the duration of rotavirus diarrhea with probiotic bacteria, while Yang et al. [91] recommended probiotic treatments for childhood rotavirus infections. Various studies have demonstrated the effectiveness of probiotic bacteria in reducing infectious diarrhea in both adults and infants. Additionally, the consumption of fermented milk by young children has been associated with a decrease in acute diarrhea (Pereg et al. 2005). Ahmadi et al. (2015) highlighted the significant positive impact of probiotics in reducing the duration of acute rotavirus diarrhea. Bifidobacterium and Lactobacillus have been linked to inhibiting rotavirus RT (Rigo-Adrover et al. 2017), and the shedding of rotavirus in outpatient children significantly decreased with the administration of Lactobacillus GG (3×10^9 cfu/g twice daily for up to 6 days) (Guarino et al. 1977).

Conclusion

Probiotics can eradicate enteric viruses by a direct and indirect mechanism. The adequacy of probiotics in the gut biological system is more pertinent since probiotics collaborate with viral diseases by a few mechanisms, containing immunomodulation, which is nearly the main component accessible for probiotics in respiratory infection. Besides, the physical connection of probiotics has been affirmed in a few examinations which affirm the limit of probiotic strains to trap infections. From the above studies, probiotics have a significant role in the immune system and also in preventing and treatments of numerous types of viruses. Little researches discuss the use of probiotics to prevent infections and treatments Covid-19. We recommended a lot of researches will test the use of many types of probiotic strains and their extract to prevent and treat Covid-19.

Key points:

- Immunological stimulation of probiotics.
- Probiotics as antiviral.
- Probiotics and COVID-19.

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