Understanding How Probiotic Bacteria Impact Viral Infections, Especially COVID-19

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Abstract

Background: In recent years, there has been a surge in scientific research focused on probiotics and their various beneficial applications. This heightened attention has led to increased awareness among scholars, government bodies, and companies operating within the pharmaceutical and food industries. Previous studies have explored the significance of probiotics, tracing their historical development and evolution**.**

Aims of the study: the current review aims to examine different aspects related to the advancing application of probiotics in combating a range of viral infections, particularly those affecting the respiratory syst

Methode: This investigation will delve into the intricate mechanisms by which probiotics act against viral pathogens and assess their potential as alternative therapeutic options for COVID-19.

Result: The eradication of such diseases may be achieved through direct probiotic administration or the incorporation of probiotic-rich foods into the
diet.

Keywords: COVID-19, Probiotic bacteria, Viral infection, Immunity, alternative therapeutical

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Introduction

The WHO defined Probiotics as live microorganisms having the ability to enhance the host, health and immunity when administered in sufficient amounts. This definition is conventional and today new nomenclatures are available in scientific publications, like ‘paraprobiotics’, which are defined as the dead or an activated probiotic. The other term is ‘postbiotics’ which is the healthy metabolites of probiotic[2]. As well as "there are basic materials called prebiotics that are consumed selectively by the host's microorganism and that provide a health benefit [3]. Many criteria can be followed to determine the probiotic properties of microorganisms, most notably,1) their ability to survive and reproduce in the digestive system, while taking advantage of the organism from its existence,2). They must be non-pathogenic and non-toxic [4]. It is more common to use different types of bacteria as probiotics, "although there are different types of microorganisms, like yeast and molds having the probiotic properties (Table1). There are many benefit can be gated form the use of probiotic [5]and [6], and these include: Improve immune system responses, vitamins synthesis, lower cholesterol levels in serum, anticarcinogenic effects, antimicrobial activities [7].

Table 1. Some examples of microbes having probiotics properties[5].

Bacteria	Yeast and molds
Lactobacillus acidophilus, sporogenes, plantarum, rhamnosum, delbrueck	Saccharomyces cerevisiae
Bifidobacterium bifidum, infantis, adolescentis, longum, hermophilum, breve	Saccharomyces bourlardii
Streptococcus lactis, cremoris, alivarius, intermedius, thermophilis, diacetylactis;	Aspergillus niger
Leuconostoc mesenteroides	Aspergillus oryzue
Pediococcus pentosaceus	Candida pintolopesii
Bacillus subtilus	Sacaromyces boulardii

2-The recent application of probiotic

Lastly, we can find an increase in the probiotic type and this increase can be related to increase the researches in this field, which in turn leads to increase in the newly discovered and identified microbes which have probiotic properties [5]. The importance of the study the probiotic bacteria leads to establish a new trend in their application far away from the traditionally one. Today, there are wide range of newly application of probiotics Table 2.

Table 2: The recent application of probiotic

Probiotic application	References
The treatment of different digestive system diseases, such as inflammatory bowel disease, irritable bowel syndrome, and necrotizing enterocolitis, necessitates individualized approaches to address each condition effectively.	8
Acute diarrhea, and antibiotic-associated diarrhea	9,10
Each of the following conditions - metabolic syndrome, obesity, atopic dermatitis, and mood disorders - requires individualized treatment approaches for effective management.	11
Prevention and treatment of viral infections (treating rotavirus infection in animals and humans)	12,13
The anti-influenza activity of a Probiotic strain derived from Bacillus subtilis.	14
Using of metabolic Products of probiotics against Transmissible Gastroenteritis Coronavirus	15
For children, prevention and treatment of respiratory tract infections.	16
Prevention of allergy	17

3-Probiotic and diseases

In recent years, significant scientific advancements have been made in exploring the connection between probiotic bacteria and various diseases . The results of studies proved that the probiotic bacteria have a role in enhancing the host's immune system, whether healthy individuals or those who suffer from various diseases [18]. The complete understanding of how probiotic bacteria work during infections remains unclear. Studies show that during infection, probiotics work to regulate the immune components and enhance the integrity of the intestinal epithelium[19], as well as organize regulatory T helper cells, type 3 natural lymphoid cells, and T cells, probiotics significantly impact mucosal immunity during the immune system's recognition of bacteria or their metabolites/products. [20]. Immunostimulatory substances such as lipoteichoic acid, peptidoglycan, and nucleic acid are found in probiotic bacteria, just like other types of bacteria., These substances exhibit similar functions to Toll-like receptor (TLR) ligands and muramyl dipeptide, acting as ligands for Nod-like receptors, These effects can be achieved through different approaches, including direct application of probiotics or the consumption of foods rich in probiotics. [21]. Recent studies have begun to focus on the mechanism of action of probiotic bacteria outside the boundaries of the digestive system[22]. Bacterial metabolism, represented by short-chain fatty acids (SCFAs) usually enhances immune response to the host, through its direct effect on both immune and epithelial cells. Studies have confirmed that SCFAs influence the pattern recognition receptor (PRR) by stimulating both NFkB, and TNF- and reducing the activation of PRR[23]. Figure 1 is an example of the role of the probiotic bacteria present in the digestive system on lung immunity. During a lung infection, probiotic bacteria in the intestine interact with Toll-like receptors (TLRs) and activate the function of both nuclear transcription factor (NFkB) and dendritic cells (DCs). T regulatory lymphocytes (Treg) are activated by dendritic cells, leading to the production of various regulatory cytokines including interleukin (IL)-10, tumor necrosis factor (TGF)-α, interferon (IFN)-γ, and IL-6.[22].

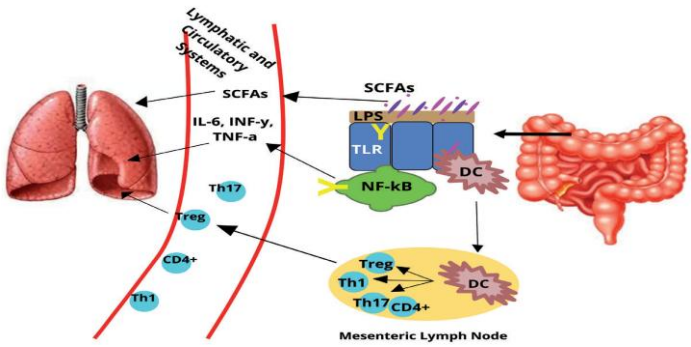

Fig. 1. A model of the role of the gastrointestinal microflora on lung immunology. [22]

4. The possibility of probiotic bacteria colonizing the upper respiratory tract

Probiotic bacteria aid and activate the immune system, regardless of whether they colonize mucous membranes. An example of this is *Lactobacillus casei*, which can fulfil its function temporarily or by impacting the existing microbial community. [24]. Therefore, a handful of trials have verified the colonization of probiotics in the top part of the respiratory system. Several studies have examined the possibility of isolating probiotic bacteria from the upper respiratory tract (Table3).

Table 3. Previous studies examining colonization of the upper respiratory tract with probiotics bacteria[25].

Topic	Planning time	Probiotic dosage	Main output	Reference
Healthy contributor, average age 38(No.6)	Taking a swab sample from the tonsils after one oral dose	L. plantarum (2 × 1011 cfu)	The colonization time is eight hours	26
Children decide for ear tubes, age from ½- 5 years (No.19)	Gathering swab samples from both the nasopharynx and tongue, after the duration of ten days.	S. salivarius K12 (1.7 × 1010 cfu)	The percentage of colonized is 33%	27
Youth adult decides to remove the tonsils, average age 24.5 years (No.57)	Sample from Tonsil tissue, three weeks	L. GG (2 × 1010cfu) or multispecies L. GG, Lc705, PJS, BB12	30-40% of participants in various intervention groups were found to have colonization in the nasal cavity.	28
Healthy adults, 30-54 years (No. 20)	Nasal spray and rhinopharyngeal swabs, three days	S. salivarius 24SMBc (8 x 109 cfu)	Initially, 95% of individuals were colonized, but after six days, only 55% remained.	29
Children decide for incision of the gland, median age 37,8 months (NO. 31)	Adenoid samples, three weeks	L. GG (8-9 × 109 cfu) × 2	100% colonized in L. GG group, 76% in placebo group	30

5. Probiotic bacteria mechanism of action in upper respiratory tract virus infections

The role of intestinal probiotic bacteria in enhancing resistance to non-enteric pathogens is currently under scrutiny, potentially attributed to their ability to bolster barrier function, generate anti-pathogenic compounds, and modulate immune responses. [31]. The antiviral action of the probiotic bacteria during viral infection is realized in many ways. First, an evolutionary antagonism relationship between bacteria and viruses is observed Scientifically proven the production of the nucleus enzyme by the probiotic bacteria which circle in both blood and lymph and is responsible for proteolysis of virion capsids [32]. Adjust the levels of pro-inflammatory cytokines IL-6, TNF-α, IL-1β, and CCL2 to mirror those found in non-infection scenarios by stimulating the expression of IFN-β and IFN-γ genes within the lungs. [33], The activity of IFN-inducible mRNAs is enhanced by increased gene expression in genes associated with antiviral functions, including Isg15, Oasl2 (2'-5' oligoadenylate synthetase-like 2), and Rsad2 (radical S-adenosyl methionine domain containing 2) [34]. By producing bacterial peptides that mimic viral peptides, Probiotic bacteria exhibit properties similar to neutralizing antibodies.)[35].finally we can summarized the probiotic mechanism of action during virus infection as in figure 2 [36].

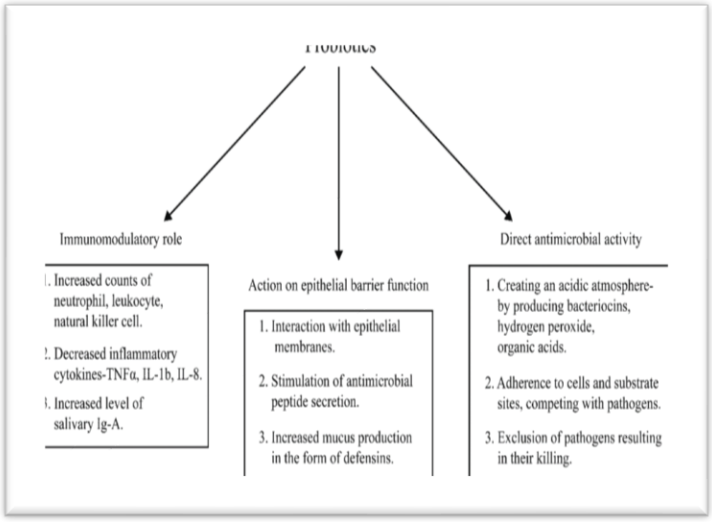

Fig. 2: How probiotics work in the respiratory tract. [36].

6. How to Link Probiotics to covid19

Covid 2019 is considered a new disease and information about its effects on the host is incomplete, and in relation to its effect on the intestinal microbiota, a dearth of data is available. The existing evidence regarding the relationship between probiotics and COVID-19 is scarce. It is unclear whether the use of probiotic supplements can serve as a preventive measure or reduce the risk of contracting the disease. [37]. Recently, Chinese study confirmed the occurrence of an imbalance in probiotics in the intestines(dysbacteriosis) of people with Covid19 with decrease account of Lactobacillus and Bifidobacterium[38]. Additionally, the study proposed the inclusion of probiotics as a supportive therapeutic method to maintain the balance of intestinal microbiota and decrease the chance of secondary infections in individuals. The results of many studies indicated that the digestive system may be one of the targets of the Corona virus, as many clinical studies confirmed that a large proportion of infected people suffer from intestinal synchronous, which is most often the appearance of diarrhea or abdominal pain [39, 40] . Additionally, infectious viruses have been identified in the stool of a COVID-19 patient exhibiting diarrhea. [41].

7- Exploring the Potential of Probiotics in COVID-19 Therapy

The recent emergence of the Covid19 and its rapid spread, which made it a global epidemic, with the announcement of the World Health Organization. And with the loss of actual treatment and the lack of a vaccine[42], Scientific research in this field is increasingly focusing on alternative approaches, whether **protective** or therapeutic, to address the disease.

. In this respect probiotic have a good attention and many researches focus on their us as alternative treatment way. There are many health benefits that can be obtained by consuming probiotics, which include avoiding seasonal illnesses, preventing infection, reducing symptoms and duration of illness [36]. Several studies were conducted to link the symptoms of Covid19 with intestinal bacteria, and the results showed that some patients experienced an imbalance of the intestinal microbiota, which was reduced by applying probiotics as additives; As a result, it decreases the chance of progressing to secondary infections, primarily attributed to bacterial translocation. [38]. There are many metabolites produced by *Lactobacillus plantarumsecretes* (Plantaricin, lactic acid, acetic acid, and gammaamino butyric acid),that have the ability to stimulate host antiviral immunity[43]. Identifying the receptors in the host cell considers the main step in infection. Thus, preventing the virus from reaching such receptors is considered an effective treatment. The SARS coronavirus (COVID-19) exerts its pathogenic effects by utilizing a mechanism where it enters cells through S proteins spike (S) and binds with host cells' Angiotensin-Converting Enzyme 2 (ACE2) receptor proteins.Researchers utilized computational techniques to design a strategy aimed at blocking the residual binding protein (RBP) found on spike proteins (S) and Angiotensin-Converting Enzyme 2 (ACE2) receptor proteins. They employed Probiotic strains, specifically Plantaricin BN, Plantaricin JLA-9, Plantaricin W, and Plantaricin D, in combination with RNA-dependent RNA polymerase (RdRp). The results of their investigation demonstrated the antiviral efficacy of the Plantaricin compounds.

Probiotics and their safe use

Using probiotics is absolutely safe, even for people who are immunocompromised or in intensive care[44]. Intensive care patients are usually very ill to receive treatment with probiotic or prebiotic, however their use in patients with upper respiratory tract infections to reduce their ventilator associated has proven effective [45],[46],and [47]. There is a live experience represented by the cohabitation of more than 65 patients suffering from serious diseases and in need of mechanical ventilation. Those patients were subjected to treatment using both bacterial probiotics(Pediococcus pentosaceus 5-33:3, Leuconostoc mesenteroides 32-77:1, L. paracasei ssp. paracasei 19, L. plantarum 2,362), in addition to prebiotics represented by(inulin, oat bran, pectin, and resistant starch).The results of these treatment were as follow: 1)reduced infection rates and inflammatory systemic response syndrome,2) reduced stays in intensive care,3) reduce days mechanical ventilation,4) the mortality rate decreased[48].

Conclusions

Probiotics are considered one of the natural alternatives therapeutic, that have proven an effective role in maintaining the general health of a healthy host as well as their effective role in reducing disease or even treating various diseases in the patient. Recently there has been an increase in research topics related to the probiotic, which has led to the discovery of newly species, as well as discovering the possibility of their presence in many different body systems far away from their natural locations represented by the digestive system. Scientific research has proven the effectiveness of probiotics in reducing or treating different viral infections, whether they are intestinal ones or those that are occurring in the respiratory infections. Recently "and after the emergence of covid-19 as a global epidemic, many studies were conducted, whether theoretical or applied one, to prove the existence of a relationship between infection with this epidemic and probiotics bacterium and the possibility of using them as part of the therapeutic alternatives after the world's inability to provide the appropriate treatment and the absence of a vaccine for this virus and the start of orientation to alternatives. Probiotics can be considered one of the successful alternatives in this field due to their effective role in strengthening the immune system. Finally, more applied research need in this field to reach accurate results, which provide the possibility of actual application of probiotic, at different levels, to control this epidemic.

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فهم كيفية تأثيربكتريا البروبيوتيك على العدوى الفيروسية، خاصة كوفيد-١٩"

المقدمة: في السنوات الأخيرة، شهدت الأبحاث العلمية زيادة كبيرة في الاهتمام بدراسة البروبيوتيك وتطبيقاتها المفيدة. وقد ساهم هذا الاهتمام المتزايد في رفع مستوى الوعي بين الباحثين والمؤسسات الحكومية والشركات العاملة في مجالات الصناعات الدوائية والغذائية. بينما ركزت الدراسات السابقة على أهمية البروبيوتيك وتتبع تطورها التاريخي.

أهداف الدراسة: تهدف هذه المراجعة إلى استكشاف مختلف الجوانب المتعلقة بالتطبيقات المتقدمة للبروبيوتيك في التصدي لمجموعة من الالتهابات الفيروسية، مع التركيز بشكل خاص على تلك التي تؤثر على الجهاز التنفسي.

طريقة العمل: تتناول الدراسة الآليات المعقدة التي تعمل من خلالها البروبيوتيك ضد الفيروسات الممرضة، مع تقييم إمكانياتها كبدائل علاجية محتملة لمكافحة فيروس COVID-19.

النتائج: يمكن تحقيق التخلص من هذه الأمراض إما عن طريق استخدام البروبيوتيك بشكل مباشر أو من خلال إدخال الأطعمة الغنية بالبروبيوتيك ضمن النظام الغذائي.