Probiotic Therapy: Critical Review of Its Implications in Fighting COVID19 And Future Perspectives

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Abstract:
In order to fight SarsCOV2 immense global grim impact and for surviving its aftereffect, search for specific effacious treatment regime is the urgent need of the hour. At this juncture, combinatorial therapeutic strategy alongside conventional treatment protocol by manipulating gut microbiota through probiotics is currently gaining considerable acceptance. The rationale of the probiotic-based therapeutic strategy is to combat pathogens in human gastrointestinal tract by use of non-pathogenic microbes, instead of synthetic drug administration. Furthermore, the concept of probiotic therapy is particularly advocated with a view to check expanding menace of multidrug resistance phenomenon. Presently, increasing number of scientific reports on complex, multifaceted interactions between human gut microbiome and the host infected with SARS COV 2 [1,2], further bolstered the concept of application of probiotics as a potential therapeutic candidate. However, views of the scientific community contradict regarding efficacy of probiotic mediated covid therapy. In a very recent report [3] Mak and Chan uphold their notion against the use of conventional probiotics to combat COVID 19. Therefore, this review probes into the scientific investigations conducted on the debated issue of applicability and aptness of probiotics administration in treating COVID19 patients. In the light of the outcomes of scientific literature reviewed here, we endorse the fact that use of probiotics has considerably alleviated some of the symptoms of COVID 19 patients and its implementation in near future should be urgently considered in developing a complimentary therapeutic strategy, strictly following the principles of evidence-based therapeutics as well as validation through clinical trials.

Keywords: COVID 19, Probiotics, immunomodulation, epigenome, therapy.

1. Introduction

Extensive explorations about the benefits obtained due to intake of probiotics has accelerated research endeavour to discover novel microorganisms to be formulated in future probiotic therapy applications to combat COVID19 [4]. Considering the gravity of the current pandemic situation worldwide and the immediate requirement to devise an effective treatment regimen for enhancing the survival rate of the COVID 19 patients, it is immensely essential to survey all the existent information. This article is framed with the notion to review the scientific evidences till date regarding the therapeutic applications of probiotics in treating COVID19 infected individuals, their translational potency to the clinics, current technology and future perspective of probiotics.

2. Historical perspectives and background/conceptualization of probiotic therapy

According to the present opinions of experts as proclaimed in a convention which took place in 2001, probiotics are defined as ‘live microorganisms which when administered in adequate amounts confer a health benefit on the host’ [5].
Recent impetus in probiotic research and commercial interest in probiotic products in the market, led to the establishment of probiotic-based therapeutic strategy an attractive alternative for treatment of various diseases. However, the concept of probiotics was already with us for long as traditional knowledge. A long time before probiotic microorganisms have become the topic of interest in the scientific community, there existed wide nutritional use of fermented products, such as cheese, bread, wine and kefir. The close association of fermented products, human health and microorganisms was initiated centuries ago. In 1857, Louis Pasteur, the famous French chemist claimed that the microorganisms are required for initiation of the fermentation process. With the advent of 20th century, the Nobel Prize winner in medicine, Ilya Ilyich Metchinkoff has correlated human health benefits with consumption of yoghurt fortified with Lactobacillus bulgaricus and Streptococcus thermophilus. In particular, he linked average long lifespan of Bulgarian peasants to their lifestyle diet which essentially included Lactobacillus containing yoghurt. Later in 1906, Henry Tissier established that clinical benefit could be obtained in infants suffering from intestinal infections by manipulating their gut microbiota and with this hypothesis; he actually paved the way for development of ‘bacterial therapy’ concept. He experimentally demonstrated that the Bifidobacterium is predominantly found in stools of healthy infants, who are breast fed and therefore advocated the use of Bifidobacterium species to treat diarrhea in infants. However at this point, there were contradictions in opinion regarding viability of therapeutic bacterial strain in extreme physiological conditions of the human gut. This difference in opinion was solved by Shirota who prepared fermented milk by using L. acidophilus shirota, which passed the test of survival along human gut passage. With this particular

invention, the concept of probiotic therapy took a major leap forward and he produced the first probiotic drink containing beneficial bacteria which gained and maintained its popularity in the market as 'Yakult', even today.
'Probiotics' is a newly coined term meaning 'for life'. Over the passage of time, the definition of 'probiotics' kept on evolving rapidly. Long ago, in 1953, the term was implemented by Kollath for the purpose of describing organic or inorganic health supplements for malnourished patients. Later, Ferdinand Vugin coined the term 'probiotika' for 'active substances contributing to healthy development of life'. The term 'probiotic' was further interpreted by Lily and Stillwell as to comprise in it the lactic acid producing bacteria which stimulates growth of different organisms. Finally the present definition of 'probiotics' was established by FAD/WHO in 2001 as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' and parameters to be followed regarding conformation test of probiotics was prepared by FAD/WHO in 2002. The term 'probiotic' is presently restricted to active, live entities that impart beneficial health characteristics to the host when consumed in a predetermined amount.

3. Search strategy: To structure the review article, PubMed (https://www.ncbi.nlm.nih.gov/ pubmed/) and Scopus (https://www.scopus.com) were utilized as scientific databases, presenting vast repertoire of information on the topic of the present paper. Search was conducted with the following search terms: "Probiotics" combined with "COVID19", "global human health", "immunomodulation", "COVID therapy", "viral infections" and "epigenomics".

3. Applications and specific therapeutic role of probiotics in COVID 19.

3.1 Immunomodulation of host system

Probiotics exert their immunomodulatory effects through various mechanisms, including the regulation of cytokines, enhancement of mucosal barrier function, and modulation of immune cell activity.
Cytokine Regulation: Probiotics have been shown to modulate the production of pro-inflammatory and anti-inflammatory cytokines by downregulating the production of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β, while upregulating the production of anti-inflammatory cytokines, such as IL-10.[6,7] This balanced cytokine response helps in reducing excessive inflammation, which is a hallmark of severe COVID-19.
Mucosal Barrier Function: The respiratory tract serves as the primary entry point for SARS-CoV-2. Probiotics can enhance the integrity of the mucosal barrier by promoting the production of mucus and strengthening tight junctions between epithelial cells.[8] This barrier function prevents the invasion of pathogens and reduces the risk of viral replication and subsequent inflammation.
Modulation of Immune Cell Activity: Probiotics can modulate the activity of immune cells, including macrophages, dendritic cells, and T cells.[9] They enhance the phagocytic activity of macrophages, promoting the clearance of pathogens. Probiotics also stimulate the maturation and activation of dendritic cells, leading to an enhanced antigen presentation and subsequent activation of T cells. These immune cell interactions contribute to a robust and balanced immune response against viral infections. Several studies have explored the use of probiotics as adjunctive therapy in COVID-19 patients. For instance, a randomized controlled trial conducted in China demonstrated that the administration of Lactobacillus acidophilus and Bifidobacterium bifidum reduced the duration of fever and improved the clinical outcomes in COVID-19 patients. Probiotics have also been shown to reduce the risk of secondary infections, such as bacterial pneumonia, which can complicate the course of COVID-19. By enhancing the mucosal barrier function and promoting the production of antimicrobial peptides, probiotics help in preventing the colonization of opportunistic pathogens.

3.2 Epigenomic regulation by probiotics

Epigenetic modulation dictates transcriptional alterations taking cues from environmental stimuli. Thus, epigenetic modification is of profound significance in mediating gut microbiota [10] and host genome interactions. Furthermore, investigation of epigenomic regulatory mechanisms would help in generation of potential therapeutic candidates to treat several disease conditions.
Probiotics, like commensal bacteria ferments the undigested food in human gut and in the process produces metabolites such as short chain fatty acids (SFCAs), the most abundant form of which is acetate, butyrate and proprionate, soluble vitamins, polyamines, polyphenols and energy metabolites.
Recently, short chain fatty acids (SFCAs) that are produced by bacteria, such as Clostridia and Bifidobacteria, from fermentation of carbohydrates and fiber have been recognized as main players facilitating crosstalk between the microbiota and host [11]. In particular, propionate, acetate and butyrate, the three most abundant SCFAs in the intestinal lumen, have received in-creasing attention in the field due to their potential beneficial impact on physiological events of the host encompassing reduced inflammation and epithelial barrier function upgradation.
The mechanistic pathways through which SCFAs are claimed to direct their actions are (a) HDAC activity inhibition, independently or along with (b) enhancing activity of G-protein coupled receptors. Currently known HDACs are subdivided into four categories based on subcellular location and yeast HDACs homology. HDACs induce tighter DNA–histone interaction and serve as transcriptional repressor marker [12].

4. Gut microbiome and their interactions with host

Recent advances in high throughput genome screening methods, 16S rRNA gene sequence based techniques have opened up a new avenue in species recognition and strain identification in human gut and their multilevel interaction with host system [13]. To rationally modulate human health through probiotics therapy, the under-spinning mechanisms behind microbiome-host interactions should be unraveled. This can be achieved by culmination of varied, high throughput data collected from metagenomics and meta-transcriptomic studies, by implementation of mathematical modeling. The gut microbiota includes a varied, complex microorganisms collection inhabiting specific niches in human gastrointestinal system.

5. Translation of probiotics to clinics

Probiotics, defined as live microorganisms that confer health benefits when administered in optimum amounts, have gained huge popularity in recent years. Their potential application in clinical settings has sparked significant interest [14], but several challenges impede the successful translation of probiotic research into effective clinical interventions. Clinical trials are vital in assessing the efficacy and safety of probiotics in different clinical conditions. Several randomized controlled trials (RCTs) have evaluated the impact of probiotics on various health outcomes, such as gastrointestinal disorders, respiratory infections, allergic conditions, and mental health. For instance, a double-blind RCT conducted by Basu et al. (2007) demonstrated a reduced duration of acute diarrhea in patients treated with *Lactobacillus rhamnosus* GG [15]. Similarly, a multicenter study by Benjak et al. (2021) observed improved symptoms of irritable bowel syndrome in subjects receiving a specific Bifidobacterium strain [16]. The lack of standardization poses challenges for probiotic therapy, hindering reproducibility and limiting interpretation of research findings. Consistency in strain identification, potency, and product formulations is essential for ensuring reliable outcomes. Several organizations, such as the International Scientific Association for Probiotics and Prebiotics (ISAPP), propose guidelines to establish standardized procedures and nomenclature. Improved standardization will enhance comparability between studies and facilitate the reliable translation of probiotics to clinical practice.

6. Safety concerns and regulatory issues

While generally regarded as safe, there are safety concerns associated with probiotic use, particularly in vulnerable populations or those with compromised immune systems [17]. The assessment of probiotic safety remains paramount to ensure their responsible application in healthcare. Studies have reported rare instances of infection and bacteremia associated with certain probiotic strains [18,19]. Therefore, it is essential to thoroughly evaluate potential risks and implement appropriate guidelines for probiotic administration, especially in individuals with underlying health conditions. To harness the potential benefits of probiotics, regulatory frameworks ensuring safety, quality, and efficacy are necessary. In many regions, including the European Union and the United States, regulatory bodies have established specific guidelines for probiotic products. Approaches such as the "Qualified Presumption of Safety" (QPS) list for microorganisms facilitate the regulatory evaluation process for certain microorganisms [20]. These measures promote accountability and facilitate the responsible translation of probiotics into clinical practice.

7. Critical assessment of current status and challenges

Currently there is immense advancement in the arena of probiotic research that can alleviate several diseases by improvement of existing microbiota of the human gut. Since aberrant gut microbiota profiles are linked with development of various lifestyle diseases like type 1 and 2 diabetes, non-alcoholic fatty liver disease, etc, therefore manipulation of gut microbiota in a beneficial way through probiotic microbes opens up a vibrant research avenue [21, 22]

However there still exist numerous challenges to overcome in the field of probiotics research even after taking into account the beneficial outcomes of probiotic therapy. Primarily, there is paucity in the information regarding the mechanistic actions of probiotics. Over usage of the probiotics might lead to sepsis or tumor development due to increased secretion of particular molecules, which though beneficial in moderate amount, may be detrimental in excess amount [23]. Hence dose optimization of probiotics is the urgent requirement. Another setback in this field is difficulty in culturing of several probiotics by conventional methods. However, with the advent and huge success of synthetic biology approach, the problem of unculturable beneficial microbes could be solved; the entire genome of a particular microbe can be biosynthetically reproduced and inserted into the desired target cells to achieve the targeted functions [24]. Adaptation of such advanced technique may pave the way of generating novel bioengineered probiotics having therapeutic importance. In addition to these obstacles in probiotic applications area, there is still room for improvement in unraveling interactions between various species of probiotic microbes and also crosstalk between individual probiotic species with the host system. More intensive investigation is needed in this aspect as several products are already available in the market comprising multiple probiotic entities with claims for synergistic beneficial effect. However, methodological interaction study among them, could actually ascertain the mode of cumulative action of these species – whether inhibitory or synergistic. Also there is lack of uniformity in selection of appropriate amount of probiotic species used in experimental studies those are widely reported to reap clinical benefits in patients. Therefore, more intensified research is required on the effect of specific probiotic strain under particular diseased condition.

8. Opinion about future directions- 'personalized probiotic profile'?

To address the challenges that impede widespread adoption of probiotics and evaluate the potential benefits of probiotic therapy in COVID-19, further research is imperative. Large-scale, well-designed randomized controlled trials (RCTs) are needed to assess the efficacy and safety of probiotics in COVID-19 management. Specific areas of focus include i. studying the effects of probiotics on SARS-CoV-2 infection and COVID-19 severity directly, through RCTs with appropriate controls. ii. identifying the most effective probiotic strains, dosage, and treatment duration for COVID-19 management. iii. exploring the potential synergistic effects of probiotics with other therapeutic interventions, such as antiviral drugs or immune-based therapies. iv. considering host-specific factors, including age, comorbidities, and immune status, to develop personalized probiotic approaches. v. assessing the impact of probiotics on long-term outcomes, including post-COVID syndrome and mental health.

9. Personalized Probiotic Profiles:

One-size-fits-all approaches to probiotic therapy may overlook the considerable inter-individual variability in gut microbial composition [3]. Personalized probiotic profiles allow for targeted interventions that address individual microbiota imbalances, promote colonization resistance, and modulate specific metabolic pathways. By considering host-specific factors, such as age, genetics, diet, lifestyle, and health status, personalized probiotic interventions can optimize microbiome-host interactions and enhance treatment outcomes.

10. Challenges in Establishing Personalized Probiotic Profiles:

Developing personalized probiotic profiles presents several challenges that necessitate further research and technological advancements in microbiome mapping, microbial interactions and standardization and quality control for strain-specific formulations for their reliable use in precision medicine.

Future advancements in technology and research will drive the development of personalized probiotic interventions:

1. Metagenomics and metabolomics: Techniques such as metagenomics and metabolomics enable a deeper understanding of the complex interactions between the host and the microbiome and thus can facilitate the identification of microbial targets and metabolite signatures for personalized probiotic interventions [25,26]. 2. Microbial databases and algorithms: Combining personalized microbiome data with comprehensive microbial databases and machine learning algorithms can enable the identification of specific probiotic strains or combinations tailored to an individual's microbiota needs [27]. 3. Fecal microbiota transplantation (FMT): FMT, the transfer of microbial communities from a healthy donor to a recipient, offers a potential avenue for personalized probiotic interventions. The selection of optimal donors based on recipient-specific characteristics can enhance FMT efficacy [28]. 4. Microbiome-based diagnostics: Developing microbiome-based diagnostic tools that assess an individual's microbial composition and functionality will aid in the selection and monitoring of probiotic interventions [29]. 5. Prebiotics and postbiotics: Personalized probiotic profiles can be complemented with prebiotics, which selectively nourish beneficial microbes, and postbiotics, the metabolic byproducts of probiotic fermentation [30]. Their combined use may enhance probiotic efficacy and individualized therapeutic outcomes.

Conclusion:

Personalized probiotic profiles offer a promising avenue for precise and customized interventions that consider an individual's unique microbiome composition and host-specific factors. By tailoring probiotic selection and formulations based on personalized microbiome profiles, optimal therapeutic outcomes can be achieved. However, challenges related to microbiome mapping, microbial interactions, lifestyle factors, and standardization must be addressed. Future directions involving advanced technologies, microbial databases, and microbiome-based diagnostics hold immense potential for advancing personalized probiotic interventions. The integration of personalized probiotics within the framework of precision medicine will pave the way for tailored therapies that harness the power of the microbiome to improve health and prevent disease.

Acknowledgements

No funding was received to produce this work.

Conflict of Interest

The author has no conflict of interest to declare.

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