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Evaluation of the Role of Probiotics in Reducing the Prevalence of Fungal and Parasitic Infections in the Gastrointestinal Tract

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Abstract

Due to their beneficial impacts on human health, including immune function as well as metabolism, probiotics, which is a colony of bacteria inhabiting the intestines and considered to be a metabolic "organ" as well. Some of the issues which they are applied in preventing and treating clinical settings are diarrhea, colon cancer, infection of Helicobacter pylori, diabetes, high blood pressure, ventilator-associated pneumonia, headaches, and autism. Probiotics might influence immunological activity through an increase in innate and adaptive immune responses, an enhancement in gut barrier function, a change in intestinal microbial habitat, a competitive adherence to the epithelium and the mucosa, and the production of antimicrobial compounds. The microbial balance in human gastrointestinal tract, a complex ecosystem, is vital to systemic health. Despite the established knowledge of the effectiveness of probiotics in counteracting the bacterial pathogens, the ability of probiotics to counteract parasitic, and fungal infections, has recently become a critical area of clinical research. This article provides a critical evaluation of how specific probiotic strains may reduce the frequency as well as the pathogenicity of protozoan parasites, such as Entameba histolytica, Giardia intestinalis, and Cryptosporidium species and eukaryotic organisms, including Candida albicans. Introducing such useful microbes into the regular treatment strategies not only addresses the increasingly problematic areas of antibiotic resistance, but also provides a long-term solution to the problem of improving gastrointestinal health in the world and reducing the number of cases concerning chronic fungal and parasitic burdens in different populations. The purpose of the presented work is identifying the need for more comprehensive research on probiotics' critical function in therapeutic use as well as prevention for various diseases which could or could not have options for treatment.

Keywords: Probiotics, Gastrointestinal tract, Fungal infections, Parasitic infections, Candida, Microbiome, Immunomodulation

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Human microbiota and beneficial bacteria

Trillions of microbes colonize the human organism. The term "microbiome" describes all the genes of microbes present in different parts of a person's body. We refer to the entirety of microorganisms that are both qualitatively and quantitatively present as microbiota. Both microbiota and human hosts, particularly the intestines, have benefited from co-evolution(1) In actuality, the host provides the intestinal microbiota with space, food, and favorable conditions to flourish, which typically contributes to the acquisition of beneficial substances and creates resistance to different infections. The human gut microbiota and host share a mutually beneficial symbiotic connection. The host provides a place for symbiotic intestinal bacteria to develop and thrive, which benefits the host's function by promoting infection resistance and aiding in the absorption of digested food (2) Thus, it seems that symbiotic bacteria and eukaryotic hosts have "co-evolved" through mutual interactions depending on mutual nutritional advantages.

Pathological conditions, like metabolic disorders or mild chronic intestinal inflammation could develop in the case when such balance is disturbed (dysbiosis) for a variety of causes, like alcohol misuse or recurrent and improper use of antibiotics(2) From birth, complex collection of microorganisms develops in the colon, a portion of gastrointestinal tract. Compared to human microbiota regarding small intestine, the large intestine's microbiota is more varied and denser. Also, the phyla Bacillota and Actinomycetota are more prevalent in intestinal samples, whereas Lachnospiracae and Bacteroidota are more prevalent in colonic samples(3) The gut microbiota of the majority of people could be divided into three major microbial groups, or "enterotypes," based on genera's prevalence, despite the wide variety of microbes that inhabit the gut: Ruminococcus (enterotype 3), Prevotella (enterotype 2), or Bacteroides (enterotype 1). Yet, more recent research indicates that there are other intermediate

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states in the gut and that the classification into three enterotypes is oversimplified. Dietary variables are the primary determinants regarding each enterotype's prevalence(2) Even while the composition could differ, it seems that everyone has a set strain of bacteria. The intestinal microbiota's primary role is protecting the intestine from pat.

Interaction between gut microbiota and host immunity

The host microbiome specifically trains and develops the host's adaptive and innate immune systems, which in turn coordinate the maintenance of crucial elements of host-microbe symbiosis(4) The intestinal immune system is composed of the gut microbiota, mesenteric lymph nodes, specialized epithelial cells, innate and adaptive immune cells, and related metabolites(5) Due to their indirect and direct interactions with host immune cells, metabolites generated by gut microbes are crucial for inflammatory signaling(6) The gut microbiota and metabolites can regulate the immune system's activity and growth of intestinal epithelial cells(7) The adaptive and innate branches of the immune system interact to protect the body from external and internal threats.

The innate immune system, which responds swiftly and widely to immunological stimuli, is considered the "first line of defense." Innate immunity includes granulocytes, macrophages, natural killer cells, and dendritic cells, which ingest pathogens and produce chemokines and cytokines. Cytokines produce lymphocytes, such as helper T cells, cytotoxic T cells, regulatory T cells (Treg cells), and B cells, which produce antibodies unique to specific pathogenic insults. These cells attract more innate immune cells and serve as the basis for adaptive immunity(8) .

Relationship between beneficial bacteria and parasitic infection

Globally, billions of people have parasitic infections. In poor nations, parasitic infections are prevalent and represent a significant public health concern(9) Helminth infections pose a serious hazard to the public health all over the world, especially in underdeveloped countries, in which socioeconomic reasons frequently lead to poor hygienic conditions(10) Intestinal protozoa are common in underdeveloped and developed countries. The most common protozoa are Toxoplasma gondii (T. gondii), Entamoeba histolytica (E. histolytica), Cryptosporidium species (sp.), Giardia (G.) intestinalis, and Blastocystis sp. Since the parasite requires a host in order to thrive, it will inevitably interact as well as come into contact with members of microbiota once it settles in human body(10) Approximately one-third of people on the planet have at least one of these protozoa. Interactions between the parasites and microbiota have the potential to significantly alter the gut's immune system as well as physical environment. The interactions could modify the pathogenicity regarding microbiota and parasites, which might change the overall disease profile and the consequences of infections(9) .

For example, in addition to interfering with the parasite's virulence and replication, microbiota could prevent the parasite from successfully colonizing the gut. This leads to a range of clinical presentations, from chronic parasite illness to asymptomatic infection(10) A parasite infection could alter the interaction of a host with its microbiota, either protecting the host from it or creating dysbiosis, which is defined as shift in microbiota's composition. When beneficial bacteria are overgrown through lesser microbes in the dysbiosis, symbiosis is disrupted and the pathology produced through parasite becomes more severe(11) In addition to influencing the pathogenicity regarding parasites, dysbiosis could lead to various illnesses, including obesity, autoimmune diseases, diabetes, cardiovascular disorders and depression. Thus, a person's overall health could be inferred from their gut health.

Relationship between beneficial bacterial and fungal infection

A group of microorganisms known as probiotics is beneficial for human health. Through their impact on the host immune system, they are frequently utilized to maintain the balance of the gut microbiome and improve intestinal health in humans(12) Contrary to popular belief, probiotics are not just bacteria; an increasing number of fungi are known to play a role in controlling the gut microbiome(13) Lactobacillus and Bifidobacterium species are the most commonly used bacterial probiotics. They are used to treat Candida albicans infections, such as oral and vaginal candidiasis There has been little research on the application of such treatments for gastrointestinal tract(14) candidiasis. In 2021, a group of researchers found that a mixture of Lactobacillus functioned as a fungicide by causing macrophages to orient toward a phenotype marked by c-type lectin receptors. By modifying inflammation and microbiota, this method manages gastrointestinal candidiasis and maintains the integrity of the gastrointestinal tract (15).

Saccharomyces cerevisiae is the most widely used fungal probiotic(16) It inhibits certain main virulence factors of Candida albicans and causes coaggregation of Candida, preventing it from adhering to epithelial cells. These include the capacity to express various aspartic proteases and the transition from yeast to hyphal form. This shortens the duration of candidiasis by accelerating the fungal clearance(17) Probiotic safety and effectiveness are guaranteed by clinical screening, which also adds evidence from subsequent human-based clinical trials. In particular, it is crucial to evaluate the advantages and disadvantages of probiotics for patients and to create customized probiotic use protocols. The main cause of vulvovaginal candidiasis, Candida albicans, presents serious health and financial challenges.

Although current antifungal drugs are highly efficient, probiotics, especially Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14, have been studied for their ability to control Candida albicans. In vitro experiments have shown the significance of lactic acid at low pH in preventing fungal proliferation, and co-cultures with lactobacilli have shown a decrease in metabolic activity and eventual elimination of C. albicans(18) Changes in gene expression were found by transcriptome analysis, which may have an effect on fluconazole resistance and shed light on the anti-virulence characteristics of probiotics against C. albicans(18) Probiotic yeasts, such as S. cerevisiae and S. boulardii, prevent Candida species, particularly C. albicans, from adhering, filamenting, and forming biofilms.

Mechanisms of interaction

Probiotics, Competitive Exclusion, and the Rationale for Evaluating Pathogen Suppression

Probiotics are considered live microorganisms that improve gastrointestinal health by altering the gut microbiota's function and composition when administered in sufficient doses(19)

Some of the interconnected processes that lead to their therapeutic effects include antimicrobial metabolite production, reinforcement of the integrity of the epithelial barrier, competition with pathogenic organisms for nutrients and adhesion sites, and regulation of host immune responses(20) Together, these processes assist in maintaining a balanced microbial community and enhance the ecological stability of the gut environment. The overall concept is that probiotics may have different contributions to a number of different microbial interactions and increase resilience as well as lessen susceptibility to pathogenic colonization, even though precise contributions regarding different pathways vary over host contexts and strains. Competitive exclusion, an ecological process by which commensal or helpful microbes exclude pathogenic organisms from establishing themselves in the gastrointestinal tract, is highly important for these interactions.

Competitive exclusion is achieved through restricting the access of pathogens to the essential nutrients, occupying ecological the niches which could be exploited by pathogens, and the production of metabolic byproducts which create poor conditions in which pathogens can proliferate(21) When such ecological barrier works well, it helps in maintaining intestinal homeostasis by allowing colonization resistance. However, every individual experiences competitive exclusion to some level. It is affected by diet, age, host health status, environmental exposures and baseline microbiota composition (22) The significance of assessing probiotic benefits over various clinical groups and study methodologies is highlighted by such sources of variability. Examples of colonization resistance disruption that may decrease competitive exclusion as well as provide ecological opportunities to the pathogenic organisms are long-term inflammation, exposure to antibiotics, immunosenescence, and changes in diet (23) These disturbances might either result in transient dysbiosis or in worse cases, a persistent microbial imbalance which makes an individual vulnerable to infections.

The use of probiotics has been proposed as a means of enhancing the function of beneficial taxa, enhancing the diversity of microbes, and preventing opportunistic pathogens in some cases to restore ecological balance. Many clinically useful probiotics, such as Limosilactobacillus, Lacticaseibacillus, and Bifidobacterium, have shown potential in enhancing immune responses, improving bowel function, and reducing inflammation(24) Nevertheless, the consistency and extent of such effects remain to be determined despite wide clinical interest. To ascertain the degree to which probiotic supplementation increases microbial diversity and decreases pathogen colonization in human populations, a systematic and quantitative synthesis of the available data is required because individual studies frequently differ in probiotic strains, dosage, and intervention duration. This approach could assist in determining whether specific intervention conditions or strains are linked to stronger competitive exclusion outcomes, evaluating the reproducibility related to probiotic effects over clinical contexts, and finding patterns that might not be apparent in individual trials.

This meta-analysis aims to provide a coherent framework for understanding probiotic-driven competitive exclusion and direct evidence-based applications concerning probiotics in the management of gastrointestinal health. Outcome measures make it difficult to draw conclusions about probiotic efficacy that are broadly applicable.

Probiotics in the Treatment of Parasitic Infections

According to the WHO, probiotics are live microbes that can improve a host's health when administered in adequate amounts(25) The majority are gram-positive bacteria isolated from the human gut microbiota or other dairy-related items, such as lassi, curds, a tasty beverage that sometimes contains cumin, and kulfi, a frozen treat from the Indian subcontinent. They are resistant to low pH and acidity and have non-pathogenic qualities. They can be purchased from pharmacies and online merchants and are available in tablet, meal, or powder form. Enterococcus, Lactobacillus, yeast, Bifidobacterium, and some fungi are the most widely used probiotics(26) Five days, or five billion colony-forming units (CFU) each day, are needed for the probiotics to outcompete the local bacteria in the gastrointestinal tract.

For probiotics to have their positive benefits, this is essential(27) Probiotics work in many ways. The mechanisms include modifying the enzyme activities that are involved in the metabolism regarding toxins as well as carcinogens, producing volatile fatty acids required in peripheral tissue function and energy homeostasis, assisting the normalization and colonization regarding disturbed gut microbes, and preventing pathogens through bacteriocin production and competitive exclusion(28) Probiotics also promote the development of mucin as well as the integrity related to intestinal barrier and controlling the function of gut-associated lymphoid tissue and immune systems(28) Probiotics could also interfere with intestinal parasites' physiology. Since their products might have antiparasitic properties and could reduce the virulence of various parasites, probiotics could be an essential part of parasitic infection management efforts(27).

Therefore, probiotics could be added to traditional antiparasitic drugs or used as antiparasitic therapy. Most published research has shown a reduction in helminth burdens when utilizing probiotic medication, although studies examining the effects of probiotics on helminth parasite infections have shown conflicting results. Certain probiotic species, such as Bifidobacterium and Lactobacillus, can protect against helminth infections by controlling the host immune system, producing antimicrobial peptides, and competing with pathogens for space and resources(25) According to multiple studies, Lactobacillus could offer protection by inducing a potent Th2 response or helminth-specific antibodies (9) Similarly, several Lactobacillus strains have been shown to inhibit protozoal parasite infection by boosting the humoral immune response against Giardia and reducing trophozoite adhesion to the mucosal surface(9).

Relationships Between Bacteria and Fungi in the Intestine

While the significance of the gut bacteriome, such as commensal species, has been thoroughly investigated, less is known about other microorganisms (29) Another significant microbial group is the gut mycobiota, which is linked to a number of host gut physiological processes, diseases, and energy metabolism (30)There has been little research on the intestinal mycobiota in livestock species, with the majority of studies concentrating on mice and humans(31) According to recent research, fungi are crucial for preserving the homeostasis of the bacterial microbiota and controlling gut health (32) Malassezia selectively produces IL-17, which is essential for coordinating the host antifungal immune response, as shown by Wheeler et al. in a murine cutaneous infection model(33) Furthermore, it was discovered that bacteria in mice stop C. albicans from growing too much, yet C. albicans could change the bacterial microbiota by, for example, promoting the growth of Bacteroides and antagonizing L. johnsonii(34).

Several studies have demonstrated the clinical significance of fungal-bacterial interactions, including bloodstream infections. For example, in cases of candidemia and bacteremia, which typically lead to severe mortality and morbidity, particularly in children, Pseudomonas and Candida species are often co-isolated (35) Additionally, dysbiosis of the bacteriome could disrupt the mycobiome in immunocompromised patients, such as those with inflammatory bowel disease (IBD) and acquired immunodeficiency syndrome (AIDS), resulting in fungal infections and worsening disease development.

According to Sokol et al.(36) fecal samples from patients with IBD had a high abundance of C. albicans and a higher Basidiomycota/Ascomycota ratio than those of healthy individuals because the distinct inflammatory environment in IBD restricts bacterial development. Furthermore, it has been demonstrated that bacteria that are common in IBD, such as E. coli, Streptococcus constellatus, and C. tropicalis, are adept at forming biofilms, which in turn stimulate one another's growth(37) In both disease and health, fungi and bacteria have intricate connections that fall into three main categories: commensalism, mutualism, and competition. Host regulation, such as immunity, can indirectly or directly realize such interactions (38).

Challenges and Limitations

Although there is an increase in awareness of microbiota-based therapies, there are many challenges and limitations in the way these therapies are widely used in clinical practice for the management of parasitic and fungal infections. Among the major challenges is the large inter-individual variability in the gut microbiota composition. Each individual harbors a different microbial profile, which is affected by diet, genetics, environment, and previous medical treatments; therefore, it is difficult to predict a consistent therapeutic outcome following the administration of probiotics. This variability tends to lead to inconsistent findings across clinical studies and restricts the generalizability of the findings (39) Another significant limitation is the lack of a clear definition of healthy or optimal microbiota. In the absence of a standardized baseline, it is difficult to determine whether a specified probiotic intervention is effective in restoring microbial balance. The gut ecosystem is dynamic and constantly changing in response to both internal and external factors, including infections resulting from fungi and parasites(40).

Moreover, the interactions among microbiota, parasites, and fungi are intricate and remain to be fully understood. These interactions comprise several mechanisms, including immune modulation, metabolic competition, and changes in the gut environment. This complexity complicates the modulation of the microbiota, resulting in either positive or unintended impacts. For example, some microbial alterations might inhibit one pathogen and inadvertently stimulate another, especially in the case of opportunistic fungi or co-infections (41) Another problem is the fact that there is a lack of quality clinical trials. Despite many in vitro and animal studies showing promising results, there have been no large-scale RCTs validating the safety and efficacy of probiotics in human populations. This lack of clinical evidence is especially apparent in parasitic infections, with most of the information remaining preliminary and not yet translated into standardized treatment protocols (42).

Furthermore, the effectiveness of probiotics is highly strain-specific. The effectiveness against particular pathogens, such as fungi and parasites, may vary among different strains of beneficial bacteria, including those of the genera Lactobacillus and Bifidobacterium. This makes it difficult to select proper probiotic formulations for clinical use and indicates the necessity to choose specific and personalized therapeutic strategies. Lastly, other limitations include dosage, length of treatment, and modes of delivery.

The best dose or treatment regimen of probiotic therapy is also not yet agreed upon, and other factors, such as survival through the gastrointestinal tract and colonization efficiency, are also of high importance in determining therapeutic success. In addition, safety issues in immunocompromised patients and the possibility of unintended microbial imbalances should be considered. Although microbiota-based therapeutics have shown tremendous potential, their clinical use in parasitic and fungal infections has yet to be translated into clinical efficacy due to biological complexity, lack of clinical evidence, and methodological issues. To address these limitations, future studies should focus on appropriately designed clinical trials, personalized microbiome approaches, and a better understanding of host-microbe-pathogen interactions.

Future Perspectives

Recent breakthroughs in the field of microbiome have provided promising opportunities for the development of microbiome-based therapies for the treatment of parasitic and fungal infections. Among the key trends is the personalization of probiotic intervention, which is supposed to target the specific composition of the gut microbial populations of the individual. Personalized methods that consider inter individual variability in the microbiota, diet, host genetics, and immune status increase the possibility of therapeutic success. Future studies will likely concentrate on combination therapies that combine probiotics with prebiotics or postbiotics to maintain long-term colonization of beneficial microbes(41).

New technologies, including metagenomic sequencing and machine learning-based predictive models, are likely to accelerate the identification of strain-specific interactions and mechanisms that modulate host immunity against pathogens (39) In addition, the clinical translation of microbiome-based interventions will increasingly depend on well-designed RCTs to prove their efficacy and safety, particularly in populations susceptible to fungal and parasitic infections. This can also include synthetic microbiota consortia designed to restore or optimize the gut ecosystem in a controlled and reproducible manner (42- 47) .Finally, future directions in microbiome-based therapy include precision and personalization, integrating the latest molecular technologies with clinical evidence to create safe and effective interventions for complex infections.

Conclusion

In conclusion, the interactions between beneficial bacteria, fungi, and parasites in the human gut are complex and dynamic. Recent studies have shown that a balanced gut microbiota is critical for maintaining host health by preventing the colonization and overgrowth of pathogenic fungi and parasites. The combination of mechanisms that provide this protective effect includes competitive exclusion, antimicrobial metabolite production, host immune system modulation, and maintenance of favorable gut environmental conditions. Moreover, any disruption of the gut microbial balance, whether through the use of antibiotics, dietary modifications, or other environmental influences, may cause an increase in susceptibility to infections. Probiotics and microbiome-targeted interventions have been shown to restore microbial equilibrium and fungal and parasitic pathogen resistance. Thus, the promotion and maintenance of a healthy gut microbiome is a promising approach for preventing and managing infections; as such, microbial diversity and stability are important for overall host defense.

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Competing Interests

The authors declare no competing interests, financial or otherwise.

Data Availability of Statement

The datasets generated and analyzed during the current study are not publicly available due to participant privacy and confidentiality concerns but are available from the corresponding author upon reasonable request.

Ethical Approval

Ethical approval for the study was provided by the relevant institutional ethics committee.

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