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Role of probiotics in prevention and control of viral infection

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Abstract
Probiotics are living microorganisms which administered in adequate amounts confer a health benefit on a host. The risk of viral infection in humans increased exponentially. However, the efficacy of vaccines and remedies for infectious disease is limited by the high mutation rate of virus, especially RNA viruses. The most common type of microbes used as probiotics are *Lactobacilli* and *Bifidobacteria*, which are generally consumed as a part of fermented foods, such as yoghurt or dietary supplements. One of the major mechanisms of probiotic action is through the regulation of host immune response. Probiotics contain immunostimulatory substances such as lipoteichoic acid, peptidoglycan and nucleic acid, which are toll-like receptor ligands, and muramyl dipeptide, which is a nod-like receptor ligand. Different experiments provide insight on the clinical effects of probiotics against respiratory virus infections. Commonly the retro viruses interact with the respiratory epithelium, which generates an innate immune response by activating the IFN signaling and other proinflammatory cytokines. Once cytokines have been secreted, macrophages and NK cells will be recruited to phagocytize and kill both viruses and viral-infected cells. To trigger a specific immune response, the immune system needs proinflammatory cytokines, energy, and some cofactor elements. Hence, probiotics can provide some elements to boost the immune response. There is another variety of mechanism to boost immune response and therefore these are also called immuno biotics. In this communication, we highlight the effectiveness of probiotics for the prevention and treatment of virally induced infectious diseases and the unique mechanism by which viruses are eliminated. Different methods and strategies such as vaccines, antibiotics, therapies, etc. have been performed for the prevention and treatment of infectious diseases but infection control has not yet been achieved at a sufficient level for diseases like Ebola haemorrhagic fever, severe acute respiratory syndrome corona virus, avian influenza, Zika virus, etc. As the increased geographical movement of humans and export and import of goods increased, the numbers of pathogenic virus species and affected area have increased. Therefore, the risk of viral infection has now become a critical issue. Most recently, scientists identified a new corona outbreak in Wuhan, China that has now reached all over the world. The virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) can cause COVID-19. Corona virus undergoes a process of discontinuous mutation as a result development of vaccine becomes difficult and the disease becomes pandemics. Corona virus typically affects the respiratory tracts of birds and mammals including humans. Doctors associate them with common cold, bronchitis, pneumonia, and severe acute respiratory syndrome. In the current studies, special emphasis is given on the viral infection and outlining the possible application of several probiotics against viral infectious disease and to explain the immune defence mechanism against viral infection that is induced by probiotics.

Keywords: Probiotics, immune response, viral infection, drugs, mutation

1. Introduction
We usually think of bacteria as something that causes diseases. But the body is full of bacteria, both good and bad. Probiotics are often called good bacteria because they help our gut healthy. The root of the word *probiotic* comes from the Greek word *pro*, meaning "promoting," and *biotic*, meaning life [1]. At the start of the 20th century, Russian noble prize winner and father of modern immunology, Elie Metchnikoff, a scientist at the Pasteur institute, was the first to conceptualize probiotics. He described the concept of probiotics in a diet containing milk fermented by *Lactobacilli*, which produce large amounts of lactic acid that could increase the life span of humans. According to the World Health Organisation (WHO) probiotics are the live microorganisms that when administered in adequate amounts confer health benefits upon the host. Probiotics are live bacteria and yeasts that are good for and have beneficial effects on the host by improving its intestinal microbial balance [2]. They are likely to have an impact through gut mucosa by balancing the local microbiota by inhibiting the growth of pathogen microorganisms and by enhancing local and systemic immune responses. The most common type of microbes used as probiotics are *Lactobacilli* and *Bifidobacteria*, which are generally consumed as a part of fermented foods, such as yoghurt or dietary supplements [3].
Various research papers and published data suggest that probiotics are able to decrease the risk

or duration of respiratory viral infection symptoms. Based on experimental studies, probiotics may exert antiviral effects directly in probiotic-virus interaction via stimulation of the immune system [4]. Several methods and strategies such as vaccines, antibiotics therapies have been applied for the prevention and treatment of infectious diseases but infection control has not yet been achieved at a sufficient level for diseases like Ebola haemorrhagic fever, severe acute respiratory syndrome corona virus, avian influenza, zika virus, etc [5]. As the geographical movement of humans and export and import of goods enhanced, the number of pathogenic virus species and affected area has also increased. Therefore, the risk of viral infection has now become a critical issue.

Most recently, authorities identified a new corona outbreak in Wuhan, China that has now reached other countries. The virus called Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) is the causative organism of COVID-19. Corona virus undergoes a process of discontinuous mutation as a result, no vaccine could be developed against the new mutated virus and it became pandemic. Corona virus typically affects the respiratory tracts of birds and mammals including humans. Doctors associate them with common cold, bronchitis, pneumonia, and severe acute respiratory syndrome.

2. Why Probiotics?

Probiotic bacteria have become increasingly popular during the last two decades as a result of the continuously expanding scientific evidence pointing to their beneficial effects on human health. Consequently, they have been applied as various products with the food industry having been very active in studying and promoting them [6]. The association of probiotics with well-being has a long history. Scientist observed that gut microbiota from healthy breast-fed infants were dominated by rods with a bifid shape (*Bifidobacteria*) which were absent from formula fed infants suffering from diarrhoea, establishing the concept that they played a role in maintaining health. The published data have coincided with the increasing consumer awareness about the relationship between health and nutrition creating a supporting environment for the development of the functional food concept introduced to describe foods or food ingredients exhibiting beneficial effects on the consumer's health beyond their nutritive value. The reported beneficial effects of probiotic consumption include improvement of intestinal health, amelioration of symptoms of lactose intolerance, respiratory tract infections and reduction of the risk of various other diseases, and several well-characterized strains of *Lactobacilli* and *Bifidobacteria* are available for human use.

3. Composition of Probiotics

Probiotics are living microorganisms promoted with claims that they provide health benefits when consumed, generally by improving or restoring the gut flora. These are beneficial components of the microbiota that have been used for centuries because of the health benefits they confer to the host. Most common microorganisms recognised as probiotics are gram-positive, with *Lactobacillus* and *Bifidobacterium* being the main species used to treat many diseases. However, some gram-negative bacteria are also used as probiotics. The best example of this group is *Escherichia coli* Nissle 1917 (EcN) also known as Mutaflor, which has been used in Germany for many years in the treatment of chronic constipation and, colitis [7]. Most bacteria are included through the fermentation process. It is a slow decomposition process of organic substances induced by microorganisms or enzymes that essentially convert carbohydrates to alcohols or organic acids. The lactic acid supplies the bacteria that then add the health benefits to the food. Some of the important foods are given below:

3.1 Kefir: This could be the most ideal probiotic dairy product because it contains both bacteria and yeast working together to provide the numerous health benefits. Kefir milk contains *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacteria* [8].

3.2 Kimchi: This fermented vegetable is made from Chinese cabbage (beachu), radish, green onion, red pepper powder, garlic, ginger, and fermented seafood (jeotgal). Many bacteria have been found to be present and can include any of the following: *Leuconostoc mesenteroides* and *Lactobacillus plantarum*, L. *mesenteroides*, L. *citreum*, L. *gasicomitatum*, L. *brevis*, L. *curvatus*, L. *plantarum*, L. *sakei*, L. *lactis*, *Pediococcus pentosaceus*, *Weissella confusa*, and *W. koreensis*. A recent review linked the health benefits of kimchi to anticancer, antiobesity, anticonstipation, colon health promotion, cholesterol reduction, antioxidative and antiaging properties, brain health promotion, immune promotion, and skin health promotion [9].

3.4 Yoghurt: It can contain *Streptococcus thermophilus*, *Lactobacillus bulgaricus* L. *acidophilus*, and *Bifidobacterium bifidum*. Research has shown links with yogurt to have positive effects on the gut microbiota and is associated with a reduced risk for gastrointestinal disease and improvement of lactose intolerance (especially among children), type 2 diabetes, cardiovascular disease, allergies and respiratory diseases, as well as improved dental and bone health [10].

3.5 Beneficial effects of probiotics in humans

Probiotics may seem new to the food and supplement industry, but they have been with us from our first breath. During a delivery through the birth canal, a newborn picks up the bacteria Bacteroides, *Bifidobacterium*, *Lactobacillus*, and *Escherichia coli* from his/her mother [11]. Probiotics protect us in two ways. The first is the role that they play in our digestion. We know that our digestive tract needs a healthy balance between the good and bad gut bacteria, so what gets in the way of this. It looks like our lifestyle is both the problem and the solution. Poor food choices, emotional stress, lack of sleep, antibiotic overuse, other drugs, and environmental influences can all shift the balance in favour of the bad bacteria. When the digestive tract is healthy, it filters out and eliminates things that can damage it, such as harmful bacteria, toxins, chemicals, and other waste products. The healthy balance of bacteria assists with the regulation of gastrointestinal motility and maintenance of gut barrier function. Research has shown some benefits for the use of probiotics for infectious diarrhea, antibiotic-associated diarrhea, gut transit, Irritable bowel syndrome (IBS), abdominal pain and bloating, ulcerative colitis, *Helicobacter pylori* infection, nonalcoholic fatty liver disease (NAFLD), and necrotizing enterocolitis [12]. The other way that probiotics help is the impact that they have on our immune system. Some believe that this role is the most important. Our immune system is our protection against germs. When it doesn't function properly, we can suffer from allergic reactions,

autoimmune disorders (for example, ulcerative colitis, Crohn's disease, and rheumatoid arthritis), and infections (for example, infectious diarrhea, *H. pylori*, skin infections, and vaginal infections). By maintaining the correct balance from birth, the hope would be to prevent these ailments. Our immune system can benefit anytime that balanced is restored, so it's never too late [13]. There are several different kinds of probiotics, and their health benefits are determined by the job that they do in the gut. They must be identified by their genus, species, and probiotic strain level. Here is a list of probiotics and their possible health benefits.

3.6 ***Lactobacillus:*** There are more than 50 species of lactobacilli. They are naturally found in the digestive, urinary, and genital systems. Foods that are fermented, like yogurt, and dietary supplements also contain these bacteria. *Lactobacillus* has been used for treating and preventing a wide variety of diseases and conditions [14]. Some of the lactobacilli found in foods and supplements are *Lactobacillus acidophilus*, L. *acidophilus* DDS-1, *Lactobacillus bulgaricus*, *Lactobacillus* GG, *Lactobacillus plantarium*, *Lactobacillus reuteri*, *Lactobacillus salivarius*, *Lactobacillus casei*, *Lactobacillus johnsonii*, and *Lactobacillus gasseri*. Studies have shown some benefits linked to *Lactobacillus* and treating and/or preventing yeast infections, bacterial vaginosis, urinary tract infection, irritable bowel syndrome, antibiotic-related diarrhea, traveler's diarrhea, diarrhea resulting from *Clostridium difficile*, treating lactose intolerance, skin disorders (fever blisters, eczema, acne, and canker sores), and prevention of respiratory infections [15].

3.7 ***Bifidobacteria*****:** There are approximately 30 species of *Bifidobacteria*. They make up most of the healthy bacteria in the colon. They appear in the intestinal tract within days of birth, especially in breastfed infants and are thought to be the best marker of intestinal health [16]. Some of the Bifidobacteria used as probiotics are *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium thermophilum*, and *Bifidobacterium pseudolongum*. Studies have shown that bifidobacteria can help with improving blood lipids and glucose tolerance. Bifidobacteria have been shown to effectively alleviate Irritable bowel syndrome (IBS) and significantly improve Irritable bowel syndrome (IBS) symptoms like pain or discomfort, distension/bloating, urgency, and digestive disorders [17].

3.8 ***Saccharomyces boulardii*****:** This is the only yeast probiotic. Some studies have shown that it is effective in preventing and treating diarrhea associated with the use of antibiotics and traveler's diarrhea. It has also been reported to prevent the reoccurrence of *C. difficile*, to treat acne, and to reduce side effects of treatment for *H. pylori* [18].

3.9 ***Streptococcus thermophilus*****:** This produces large quantities of the enzyme lactase, making it effective, according to some reports, in the prevention of lactose intolerance [19].

4. Beneficial effects of probiotics in animals

Probiotic use in animal nutrition is widely accepted today. Rapid advancements in molecular biology and gene sequencing are helping researchers dig deep on finding new probiotic applications for animals, including in feed and in consumer-packaged health products for companion pets [20] Companion animals like dogs and cats are usually on high-carbohydrate diets. Similar to humans, their health and well-being depends on their gut microbe communities. Probiotic bacteria strains help maintain healthy levels of good bacteria in the gastrointestinal tract, defending the gut against pathogenic bacteria. Probiotic ingredients also include spore formers and yeast-based ingredients. These additives help in vitamin production, management of toxins, destruction of harmful bacteria, effective digestion of fibers, and increased absorption of nutrients [21].

4. Livestock nutrition

Over the last decade or so, there has been a significant rise in the adoption of probiotics in animal feed for farm animals like swine, cattle, horse, ruminants, and poultry. Using probiotics in cattle feed has shown beneficial results in terms of animal performance, digestion, and the immune system [22]. The bacteria most commonly used as animal-feed probiotics include *Lactobacillus, Bacillus, Streptococcus, Pediococcus* and *Bifidobacterium*. Most commercially available probiotics contain more than one species for maximum effect. Some also contain fungi and yeast stains. The live cultures used in probiotics are available in vegetative form and spore form. Vegetative cultures are humidity and heat sensitive, while spore cultures are naturally strong when it comes to withstanding heat, antibiotics, and stomach acid [23].

5. The future of animal probiotics

High probiotic demand from cattle farmers and the companion animal sectors are expected to boost the adoption of advanced probiotic technologies. Top players are investing hefty amounts in research and development to discover entirely novel products and applications. Nano encapsulated probiotics are expected to create numerous opportunities for the industry in near future. Apart from being gut flora stabilizers, probiotics are expected to be utilized for more applications in animals, including for increased immunity and reduced stress levels. Probiotics will also continue to be used to improve the quality of eggs and meat and can reduce salmonella. And, overall, the microorganisms used in probiotics are approved for animal nutrition and do not constitute a major hazard for animal health. They do not affect metabolic processes of animals as they are not transferred from intestines to other body parts.

6. Protective evidences of probiotic *in viral* infection

Viral respiratory infections are the most common diseases in humans. Many experimental studies *in vitro* and in animals show that specific strains of probiotics are capable of providing protection against viral infections by stimulating antiviral, cytokine, and chemokine responses in the respiratory and gastrointestinal epithelial cells or immune cells[24].Data from animal studies indicate that strains of lactobacilli and bifido bacteria provide protection against respiratory virus infections also by inducing the synthesis of virus-specific immunoglobulins in the respiratory secretions and in serum. In addition, studies in healthy human subjects suggest that specific probiotics may enhance the immunogenicity of viral vaccines [25]. L. *rhamnosus* GG was effective in inducing protective immune response against the H_3N_2 strain in influenza virus vaccine [26]. *Moreover* L. *fermentum* CECT5716 ingestion in adults resulted in lower influenza-like illness, increased proportion of NK cells in blood, significantly higher TNF-α, and increased anti-

influenza-specific IgA and IgM after influenza vaccination. The consumption of *B. animalis* sp. *lactis* Bb12 or L. *paracasei* sp. *paracasei* L. *casei* 431431 also showed significantly greater increase in influenza virus vaccine-specific IgG antibodies in plasma and secretory IgA in saliva [27].

Probiotics are frequently part of the normal gastrointestinal microbiota, and, therefore, probiotic therapy is generally considered as safe [28].

7. Mechanism of probiotic action

Some probiotics have shown an antiviral activity and several mechanisms have been demonstrated. In respiratory tract infections (RTI), the majority of probiotics can inhibit the most important respiratory viruses (RV) by immunomodulatory mechanisms. This antiviral mechanism might be explained due to the entry routes of RV. RVinfects the mucosal cells of the RT, and for this reason, probiotic strains and their antimicrobial compounds cannot directly interact with viruses by physical contact [29]. Probiotic strains finally reduce or eradicate virus infectivity by immunomodulatory activity, which has led scientists to call them immuno biotics Probiotics can inhibit viruses and help the immune system defend itself against RV. First, the RVs interact with the respiratory epithelium, which generates an innate immune response by activating the IFN signaling and other proinflammatory cytokines [30]. Once cytokines have been secreted, macrophages and NK cells will be recruited to phagocytize and kill both viruses and viral-infected cells. To trigger a specific immune response, the immune system needs proinflammatory cytokines, energy, and some cofactor elements. Hence, probiotics can provide some elements to boost the immune response. Probiotics interact with the gut epithelium and are recognized by Intestinal Dendritic Cells (IDC); this interaction results in the production of IL-12 and IFNγ by which can modulate both the respiratory and gut immune response [31].Secretion of IFNγ and IL-12 by intestinal dendritic cells; these two proinflammatory cytokines have dual functions: IFNγ and IL-12 can circulate in the bloodstream to reach the respiratory epithelium and therefore help alveolar macrophages and NK cells eliminate RV [32]. The proinflammatory cytokines (IFNγ and IL-12) secreted in the gut ecosystem after colonization of some probiotic strains help the immune system to generate a specific Th1/Th17 immune response; the number of CD4+ and CD8+ increases and becomes more efficient. In addition, CD4+ will secrete IL-17, which enhances the innate immune response [33]. Some probiotic strains, via induction of IFNγ and IL-17 production, can stimulate the over expression of innate immunity-related genes such as the over expression of Toll-like Receptor7 (TLR7), even in the lung. This over expression of TLR7 amplifies the innate immune responses [34]. Probiotics can help B lymphocytes differentiate and become plasma cells, which can secrete specific IgA. Some studies showed the impact of some probiotics in increasing IgA in lung tissues. However, until now there is no explanation of the real mechanisms of how intestinal probiotics can help secretion of IgA which are specific to elimination of RVs. This effect can be explained by the capacity of some probiotics to enhance cytokine production, which can improve the rapid differentiation of B lymphocytes to plasma cells in lung tissues [32-33].

8. Probiotics and Corona virus

In 2019, the Centers for Disease Control and Prevention (CDC) started monitoring the outbreak of a new corona virus, SARS-CoV-2, which causes COVID-19. Authorities first identified the virus in Wuhan, China. Since then, the virus has spread to nearly every country, leading the WHO to declare a pandemic. COVID-19 presents with a spectrum of disease severity, ranging from mild and non-specific flu like symptoms, to pneumonia, and life-threatening complications such as acute respiratory distress syndrome (ARDS) and multiple organ failure [35]. While transmission of SARS-CoV-2 is thought to occur mainly via respiratory droplets, the gut may also contribute toward the pathogenesis of COVID-19. SARS-CoV-2 RNA has been detected in the gastrointestinal tract and stool samples from patients, and in sewage systems. Coronaviruses, including SARS-Cov-2 can invade enteroocytes, thereby acting as a reservoir for the virus. Indeed, large clinical studies from China indicate that gastrointestinal symptoms are common in COVID-19, and are associated with disease severity [36]. Clinical evidence shows that certain probiotic strains help to prevent bacterial and viral infections, including gastroenteritis, sepsis, and respiratory tract infections (RTIs). The reason for adding probiotic strains to the overall prevention and care strategy is founded in science and clinical studies. The gut microbiome has a critical impact on systemic immune responses, and immune responses at distant mucosal sites, including the lungs. Administration of certain *Bifido bacteria* or *lactobacilli* has beneficial impact on influenza virus clearance from the respiratory tract. Probiotic strains improve levels of type I interferons, increase the number and activity of antigen presenting cells, NK cells, T cells, as well as the levels of systemic and mucosal specific antibodies in the lungs [37].There is also evidence that probiotic strains modify the dynamic balance between proinflammatory and immunoregulatory cytokines that allow viral clearance while minimizing immune response-mediated damage to the lungs. This might be particularly relevant to prevent ARDS, a major complication of COVID-19. An Randomised Control Trial (RCT) with Lactobacillus plantarum DR7 showed suppression of plasmapro-inflammatory cytokines (IFN-γ, TNF-α) in middle-aged adults, and enhancement of anti-inflammatory cytokines (IL-4, IL-10) in young adults, along with reduced plasma peroxidation and oxidative stress levels. Given the cytokine storm that appears to occur in many COVID-19 patients, this type of modulation may prove to be very important. The manner in which orally administered probiotic strains contribute to this appears to involve the immune response emanating from the intestine, a focal point of the body's defences. Therefore, probiotic strains documented to enhance the integrity of tight junctions, for example through increasing butyrate, a fuel for colonocytes could theoretically reduce SARS-Cov-2 invasion [36]. Evidence for antiviral activity of probiotic strains against common respiratory viruses, including influenza, rhinovirus, and respiratory syncytial virus comes from clinical and experimental studies. While none of these effects or mechanisms has been tested on the new SARS-CoV-2 virus, this should not negate considering this approach, especially when effects of probiotics against other corona virus strains have been reported.

Probiotic microorganisms will form the system each at the native and general level which can permit future probiotics as treatments for several diseases. Probiotics appear to own promising role in shortening length of infections or decreasing susceptible to the pathogens [38]. Use of the various strains, dosage, and length of treatment and smaller size of the trials makes interpretation of the offered information harder.

probiotic effects area strain-specific, and not act through constant mechanisms. It's needful to find there area unit optimum probiotic species, doses, and/or formulations. Though the information with probiotics still too weak to convert into clinicians. Technology of probiotics is of rising interest and exposes new potentialities for the probiotics applications. Their applications to the agriculture and food sector area are comparatively recent compared with their use in drug delivery and prescription drugs [39].

9. Conclusion

There have been several clinical reports regarding the use of probiotics for the prophylaxis or treatment of infectious diseases. Here, we reviewed the literature regarding several probiotics agents based on the papers which described single probiotics in clinical trial to avoid the crosstalk or mutual interference between probiotics. Such agents are considered to be safe, affordable and easy to consume because of their long history of use in foods. Probiotics exhibit direct and indirect mechanisms in eradicating enteric viruses. The effectiveness of probiotics in the gut ecosystem is more relevant, since they interact with viral infections by several mechanisms, including immunomodulation. The state of knowledge regarding the immunomodulatory effects of probiotics has recently advanced and various studies have especially focused on the interactions between commensal bacteria and the mucosal immune system. Furthermore, the role of type 1 IFNs in the elimination of pathogenic viruses, which involves the concerted activities of the innate and acquired immune systems, has been widely studied. Although further detailed research is necessary, probiotics are expected to be the rational adjunctive options for the treatment and prophylaxis of viral infections.

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