ISSN: 2349-9818
March- April 2020, Vol. 7 (2), 01-14

Tropical Journal of Pharmaceutical and Life Sciences
(An International Peer Reviewed Journal)
Journal homepage: http://informativejournals.com/journal/index.php/tjpls

Review Article

A COMPREHENSIVE REVIEW OF PROBIOTICS AND THEIR USES FOR CONTROL OF VIRAL INFECTIONS IN THE WAKE OF PANDEMIC COVID-19

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Received: 30 March 2020; Revised: 5 April 2020; Accepted: 16 April 2020; Published: 21April 2020

ABSTRACT

In this review, an attempt is made to comprehensively study the effectiveness of probiotics for the prevention and/or treatment of viral infectious diseases, which may be useful to combat the new corona virus. This review will provide an overview of the unique mechanism by which viruses are eliminated through the stimulation of type 1 interferon production by probiotics via the activation of dendritic cells.

Till today, there are no specific vaccines or treatments for COVID-19. However, there are many ongoing clinical trials which are evaluating potential agents for treatment. Corona virus disease (COVID-19) is an infectious disease caused by a newly discovered corona virus named as SARS Corona virus-2. The pathophysiology of COVID-19 clearly indicate the sensitivity of SARS CoV-2 to IFN. Reports on treatment of COVID-19 patients with IFN shows positive results. Considering the proven antiviral and immunomodulatory activity of probiotics and ability to stimulate interferon production, it is recommended to use probiotics as the adjunctive therapy for the prophylaxis of COVID-19. The ongoing pandemic has upturned the whole world socially and economically. Although further detailed research is necessary in the future, probiotics are expected to be among the rational adjunctive options for the treatment of Corona viral diseases.

Keywords: Probiotics, COVID-19, SARS Corona virus infection, Interferon, Dendritic cell, Adjunctive therapy.

INTRODUCTION

Infection control has not yet been achieved at a sufficient level even after the advancement of medical sciences .Various strategies, such as using vaccines and antibiotics, have been exploited for the prevention and treatment of infectious diseases, but every year new emerging and re-emerging infectious diseases spurt and create epidemics and pandemics, the latest is COVID-19. In addition avian influenza, severe acute respiratory syndrome, Ebola hemorrhagic fever, dengue fever and Zika virus infection, Nipah viruses etc also are nightmare for medical professionals.

Climate changes including global warming and the increased geographical movement of people and goods, deforestation are some of the reasons for emergence of the numbers of pathogenic virus species. Therefore, the risk of viral infection has now become a critical issue. Virus sometimes undergoes a process of discontinuous mutation.

As a result, the efficacy of vaccines against influenza virus may become disrupted, and this phenomenon has sometimes caused pandemics.[1]

COVID-19 is the new pandemic which is caused by a novel corona virus. Corona viruses are a large family of viruses, some of which cause illness in people, and others that circulate among mammals and birds. Rarely, animal corona viruses can spread to humans, and then spread between people. Zoonotic corona viruses have emerged in recent years to cause human outbreaks such as severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). COVID was first identified in Wuhan City, Hubei Province, China, in December 2019. Since then it has spread to many countries around the world, with the World Health Organization declaring it a pandemic. The case fatality rate is approximately 2.3% (based on initial information). Initially, the new virus was called 2019-nCoV. Subsequently, the task of experts of the International Committee on Taxonomy of Viruses (ICTV) termed it the SARS-CoV-2 virus as it is very similar to the one that caused the SARS outbreak (SARS-CoVs).[2]

As per WHO "Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. The best way to prevent and slow down transmission is be well informed about the COVID-19 virus, the disease it causes and how it spreads. Protect yourself and others from infection by social distancing and washing your hands or using an alcohol based rub frequently and not touching your face.[3] There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock. In this scenario, professionals are suggesting various alternative medicines like Ayurveda, Siddha, Herbal medicines and other adjunctive therapeutic methods to control COVID-19. In this review, an attempt is made to comprehensively study the effectiveness of probiotics for the prevention and/or treatment of virally induced infectious diseases which may be useful to combat the new corona virus.

Probiotics

Probiotics were earlier defined as non-pathogenic microorganisms which when ingested, exert a positive influence on host's health or physiology. The latest definition put forward by FDA and WHO jointly is "Live microorganisms which when administered in adequate amounts confer a health benefit to the host".

Some of the popularly used probiotic microorganisms are *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, Bifidobacteria and certain strains of *Lactobacillus casei*, Lactobacillus acidophilus-group, Bacillus coagulans, *Escherichia coli* strain Nissle 1917, certain enterococci, especially *Enterococcus faecium* SF68, and the yeast Saccharomyces *boulardii*. Bacterial spore formers, mostly of the genus Bacillus dominate the scene.

These probiotics are added to foods, particularly fermented milk products, either singly or in combinations. New genera and strains of probiotics are continuously emerging with more advanced and focused research efforts. Probiotics possess important functional attributes that could fulfil most of our basic nutritional and clinical supplementation requirements. These microbes have shown positive responses to clinical treatment against several diseases and disorders, such as diarrhoea associated with rotavirus, IBS and food allergies. Moreover, the contribution of probiotics in preventing and treatment of diabetes, obesity, cancer and diseases related to pathogenic microbes is an exciting and rapidly advancing research arena.

Dietary probiotic supplementation generally involves dairy products but probiotics can also be incorporated into non-dairy fermented food products, presenting an alternative and more advantageous source in the process of evaluating new probiotic strains. Moreover, present clinical and nutritional evaluations have been successful in exposing some remarkable functions of particular probiotic strains. Specifically, regulation of energy in various catabolic and anabolic processes, acid and bile tolerance, ability to adhere to gut epithelial cells, to combat against pathogens, along with certain other properties, like their safety-enhancing property, serviceability as food and beneficial supplements for human health. Therefore, current focus is on evaluating new strains of probiotics and their applicability in biomedical/clinical research, paving a new direction for exploration and exploitation of probiotics aimed at improving human health.[4]

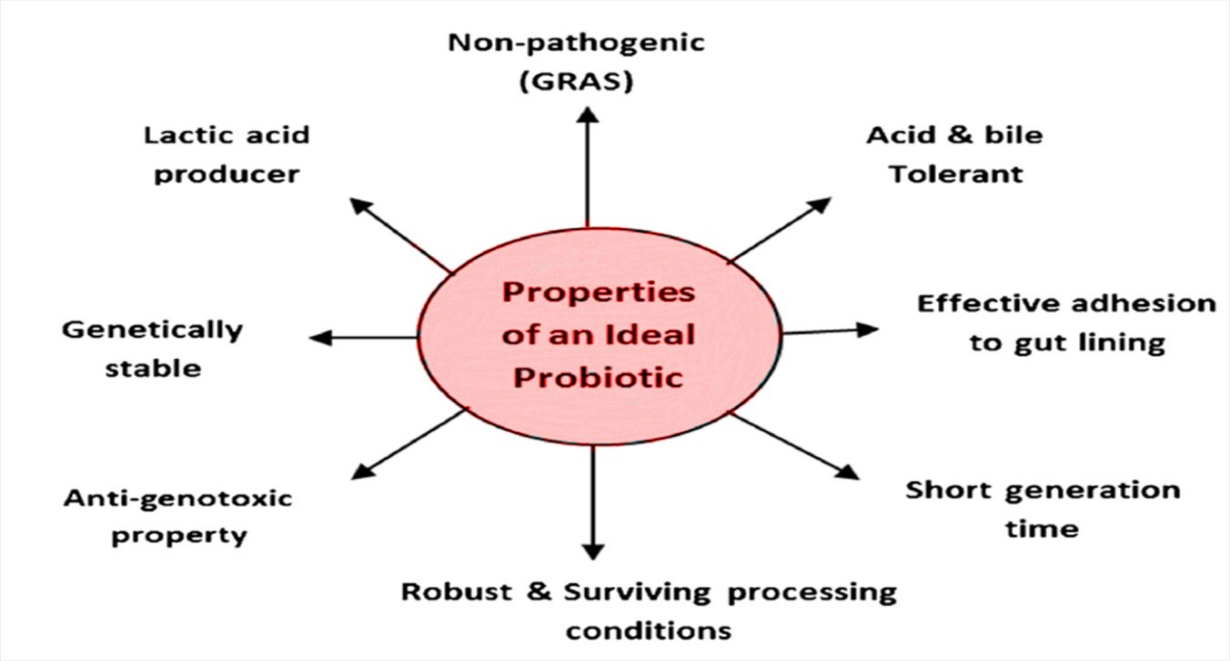

Figure1: Characteristics of an ideal probiotic strain

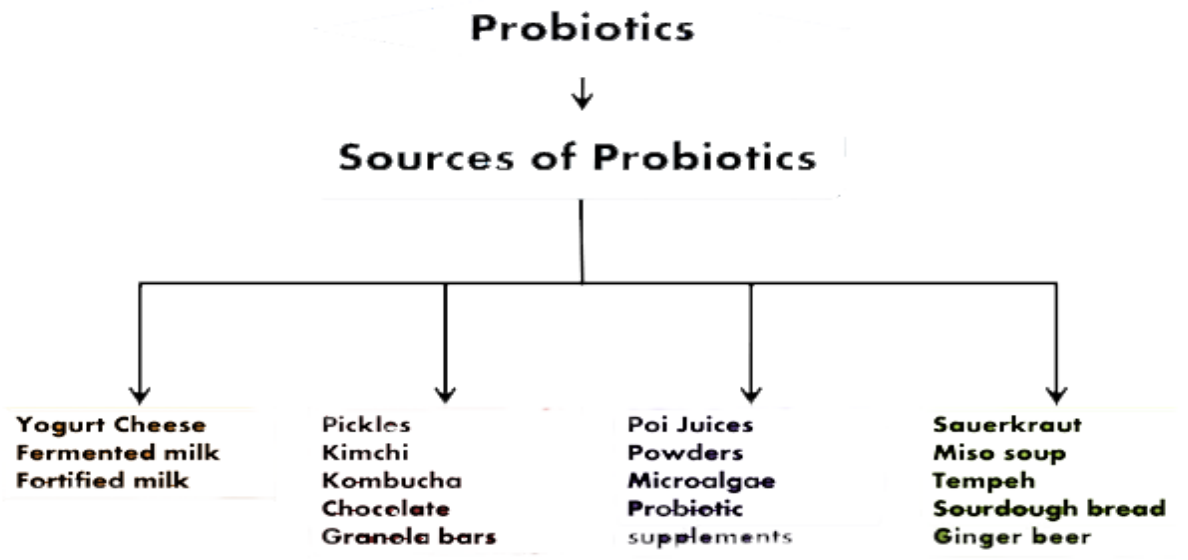

Figure 2: Different sources of probiotics

Prebiotics and Symbiotics

Other two terms associated with probiotics are Prebiotics and symbiotics. Prebiotics are mostly "fibres that are non-digestible food ingredients" and beneficially affect the host's health by selectively stimulating the growth and/or activity of some genera of microorganisms in the colon, generally lactobacilli and Bifido bacteria an ideal prebiotic should be 1) Resistant to the actions of acids in the stomach, bile salts and other hydrolyzing enzymes in the intestine 2) Should not be absorbed in the upper gastrointestinal tract. 3) Be easily fermentable by the beneficial intestinal microflora . Prebiotics like inulin and pectin exhibit several health benefits like reducing the prevalence and duration of diarrhoea, relief from inflammation and other symptoms associated with intestinal bowel disorder and protective effects to prevent colon cancer. They are also implicated in enhancing the bioavailability and uptake of minerals, lowering of some risk factors of cardiovascular disease, and promoting satiety and weight loss thus preventing obesity.

Synbiotics are combination of prebiotics with probiotics. A synbiotic product beneficially affects the host in improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract by selectively stimulating the growth and/or activating the metabolism of one or a limited number of health promoting bacteria. Because the word synbiotics alludes to synergism, this term should be reserved for products in which the prebiotic compounds selectively favor the probiotic organisms. Synbiotics were developed to overcome possible survival difficulties for probiotics. It appears that the rationale to use synbiotics, is based on observations showing the improvement of survival of the probiotic bacteria during the passage through the upper intestinal tract. A more efficient implantation in the colon as well as a stimulating effect of the growth of probiotics and ubiquitous bacteria contribute to maintain the intestinal homeostasis and a healthy body.

Health benefits of probiotics, probiotics and synbiotics are important and documented beneficial effects of probiotics include the prevention of diarrhoea, constipation, changes in bile salt conjugation, enhancement of antibacterial activity, anti-inflammatory. Furthermore, they also contribute to the synthesis of nutrients and improve their bioavailability; some probiotics are known to exert anti-oxidative activity in the form of intact cells or lysates. Probiotics have also demonstrated their inherent effects in alleviating symptoms of allergy, cancer, AIDS, respiratory and urinary tract infections. There are stray reports on their beneficial effects on aging, fatigue, autism, osteoporosis, obesity and type 2 diabetes.[5]

As shown below a number of mechanisms are thought to be associated with probiotic beneficial effects:

- Produce inhibitory substances like H2O2, bacteriocins, organic acids, etc.
- Block adhesion sites for pathogenic bacteria.
- Competition with the pathogenic bacteria for nutrients.
- toxin Degradation and blocking of toxin receptors,
- Modulation of immune responses

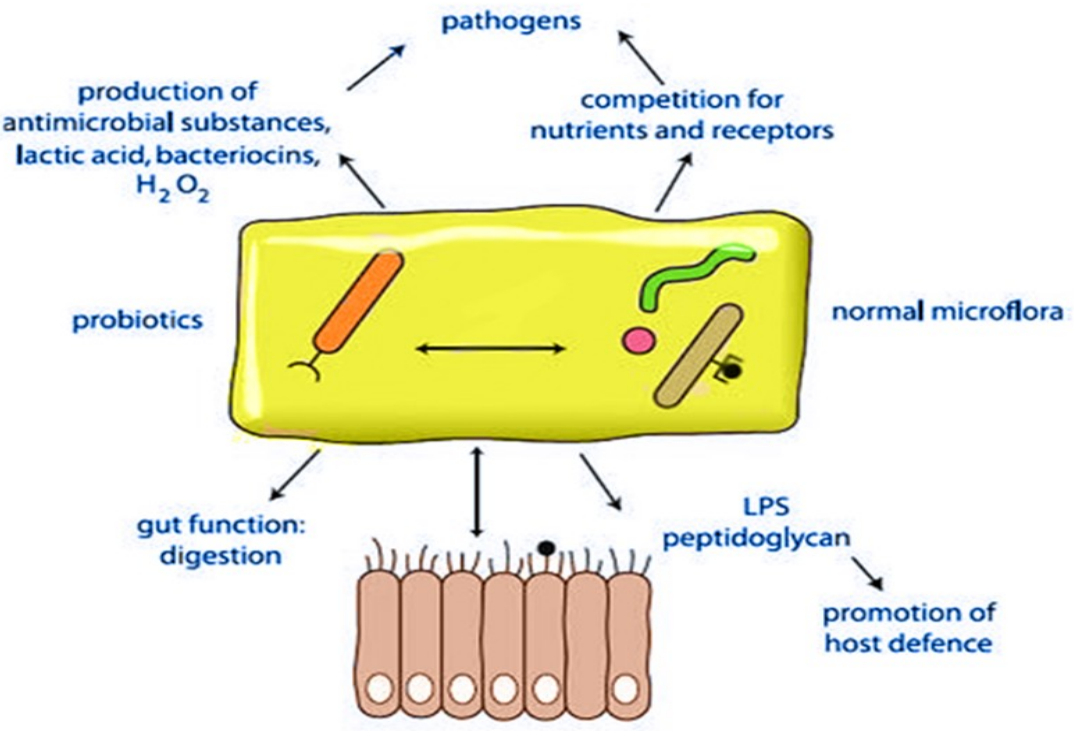

Figure 3: Mechanism of action of Probiotics

Pathophysiology of COVID-19

CoVs are enveloped, positive-stranded RNA viruses with nucleocapsid. In CoVs, the genomic structure is organized in a +ssRNA of approximately 30 kb in length — the largest known RNA viruses — and with a 5′-cap structure and 3′-poly-A tail. Starting from the viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized. Different CoVs present special structural and accessory proteins translated by dedicated sgRNAs.[6] Pathophysiology and virulence mechanisms of CoVs, and therefore also of SARS-CoV-2 have links to the function of the nsps (non structural proteins) and structural proteins. For instance, research underlined that nsp is able to block the host innate immune response. Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. However, many of these features (e.g., those of nsp 2, and 11) have not yet been described.[7]

Among the structural elements of CoVs, there are the spike glycoproteins composed of two subunits (S1 and S2). Homo trimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors. Of note, in SARS-CoV-2, the S2 subunit — containing a fusion peptide, a transmembrane domain, and cytoplasmic domain — is highly conserved. Thus, it could be a target for antiviral (anti-S2) compounds. On the contrary, the spike receptor-binding domain presents only a 40% amino acid identity with other SARS-CoVs. Other structural elements on which research must necessarily focus are the ORF3b that has no homology with that of SARS-CoVs and a secreted protein (encoded by ORF8), which is structurally different from those of SARS-CoV.

In international gene banks such as GenBank, researchers have published several Sars-CoV-2 gene sequences. This gene mapping is of fundamental importance allowing researchers to trace the phylogenetic tree of the virus and, above all, the recognition of strains that differ according to the mutations. According to recent research, a spike mutation, which probably occurred in late November 2019, triggered jumping to humans. In particular, Angeletti et al. compared the Sars-

Cov-2 gene sequence with that of Sars-CoV. They analyzed the transmembrane helical segments in the ORF1ab encoded 2 (nsp2) and nsp3 and found that position 723 presents a serine instead of a glycine residue, while the position 1010 is occupied by proline instead of isoleucine. The matter of viral mutations is key for explaining potential disease relapses.[8]

Research will be needed to determine the structural characteristics of SARS-COV-2 that underlie the pathogenetic mechanisms. Compared to SARS, for example, initial clinical data show less extra respiratory involvement, although due to the lack of extensive data, it is not possible to draw definitive clinical information.

The pathogenic mechanism that produces pneumonia seems to be particularly complex. Clinical and preclinical research will have to explain many aspects that underlie the particular clinical presentations of the disease. The data so far available seem to indicate that the viral infection is capable of producing an excessive immune reaction in the host. In some cases, a reaction takes place, which as a whole is labelled a 'cytokine storm'. The effect is extensive tissue damage. The protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells, and inhibits the growth of others. It also stimulates the production of acute phase proteins and plays an important role in thermoregulation, in bone maintenance and in the functionality of the central nervous system. Although the main role played by IL-6 is pro-inflammatory, it can also have anti-inflammatory effects. In turn, IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases and some types of cancer. It is also implicated into the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.[9]

Treatment / Management of COVID-19

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock.

On January 28, 2020, the WHO released a document summarizing WHO guidelines and scientific evidence derived from the treatment of previous epidemics from HCoVs. This document addresses measures for recognizing and sorting patients with severe acute respiratory disease; strategies for infection prevention and control; early supportive therapy and monitoring; a guideline for laboratory diagnosis; management of respiratory failure and ARDS; management of septic shock; prevention of complications; treatments; and considerations for pregnant patients.[10]

Other Therapies for COVID-19

Among other therapeutic strategies, systemic corticosteroids for the treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) are not recommended. Moreover, unselective or inappropriate administration of antibiotics should be avoided, although some centres recommend it. Although no antiviral treatments have been approved, several approaches have been proposed such as lopinavir/ritonavir (400/100 mg every 12 hours), chloroquine (500 mg every 12 hours), and hydroxychloroquine (200 mg every 12 hours). Alpha-interferon (e.g., 5 million units by aerosol inhalation twice per day) is also used. Preclinical studies suggested that remdesivir (GS5734) — an inhibitor of RNA polymerase with in vitro activity against multiple RNA viruses, including Ebola — could be effective for both prophylaxis and therapy of HCoVs infections. This drug was positively tested in a rhesus macaque model of MERS-CoV infection.

In Italy, a great investigation led by the Istituto Nazionale Tumori, Fondazione Pascale di Napoli

is focused on the use of tolicizumab. It is a humanized IgG1 monoclonal antibody, directed against the IL-6 receptor and commonly used in the treatment of rheumatoid arthritis.[11] When the disease results in complex clinical pictures of MOD, organ function support in addition to respiratory support, is mandatory. Extracorporeal membrane oxygenation (ECMO) for patients with refractory hypoxemia despite lung-protective ventilation should merit consideration after a case-by-case analysis. It can be suggested for those with poor results to prone position ventilation.

Prophylaxis and Treatment of Infectious Diseases by Probiotics

Progress of research on the relationship between the microbes and illness, commensal intestinal bacteria have been investigated for their ability to modulate the immune response, not only in healthy individuals but also in those who are suffering from a wide range of diseases. It has been noted that commensal bacteria also regulate regulatory T cells, type 3 innate lymphoid cells, and T helper cells through the recognition of the bacteria themselves or their metabolites/products by the immune cells and greatly affect mucosal immunity. This immune modulator activity can be used for the therapeutic purpose of COVID-19.

Probiotics act on both the innate and acquired immune systems and have the potency to reduce the severity of infections in the gastrointestinal and upper respiratory tracts. Data shows that 50 percent of COVID-19 patients are having gastrointestinal complications. Probiotics are defined as “live microorganisms that have health benefits for the host”, and they are generally consumed as a component of fermented foods such as yoghurt, cheese, and pickles or as supplements. Recently, “ghost probiotics” or paraprobiotics were reported to retain their immune modulatory potency beyond their viability. Probiotics contain immune stimulatory substances such as lipoteichoic acid, peptidoglycan, and nucleic acid, which are Toll-like receptor (TLR) ligands, and muramyl dipeptide, which is a Nod-like receptor ligand.[12] The representative probiotics(Bacterial strains) that have shown unique preventive or therapeutic capacities against viral diseases in clinical studies are listed below.

1. Lactobacillus casei Shirota (LcS)

LcS reduced plasma antibody titers in cytomegalovirus and Epstein–Barr virus infected highly physically active people (university athletes). But no significant difference in the incidence of norovirus-induced gastroenteritis between the LcS and control groups in long-stay elderly people. Although the effectiveness of LcS remains controversial, a potential mechanism was reported wherein LcS was found to modulate the activity of natural killer (NK) cells.[13,14]

2. Lactobacillus rhamnosus (LGG)

The preventive effects of LGG on experimental rhinovirus infections in healthy volunteers were evaluated. The frequency and severity of cold symptoms and the number of subjects with rhinovirus infection in the LGG group were lower than those of the control group, although the difference between the groups did not reach significance. When LGG was administered for 4 weeks to children with gastroenteritis who were positive for either rotavirus or Cryptosporidium species in stool, a significant increase in serum immunoglobulin (Ig)G levels post-intervention was observed in children with rotavirus-induced diarrhea who received LGG. Among the children with cryptosporidial diarrhea, those receiving LGG showed a significant improvement in intestinal permeability. The mechanisms by which probiotics exert immune-modulatory effects are not completely understood. However, LGG was demonstrated to modulate the innate and adaptive immune responses, resulting in increased levels of serum IgG and secretory IgA targeting enteric pathogens like rotavirus.[15,16]

3. Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1 (R-1)

A study demonstrated that the consumption of yoghurt fermented with R-1 augmented NK cell

activity and reduced the risk of catching the common cold in elderly individuals. Other studies showed that R-1 and its secreted polysaccharides improved immune system functions accompanied by the activation of NK cells. Thus, R-1 or its products might contribute to the prevention of respiratory infections caused by respiratory or influenza viruses.[17,18]

4. Lactobacillus paracasei ssp. paracasei (L. casei 431)

L. casei 431 was reported to have the ability to shorten the duration of upper respiratory symptoms, although it showed no effect on the immune response to influenza vaccination in healthy adults . In another study, L. casei 431 was demonstrated to modulate the immune system using a vaccination model in healthy subjects. Increase from baseline in the titers of vaccine-specific IgG, IgG1, and IgG3 in plasma as well as that of vaccine-specific secretory IgA in saliva were significantly greater in both probiotic groups, as compared with the control group. This probiotic stimulates the innate viral defense mechanisms and reduces inflammation in the host.[19,20]

5. Lactobacillus paracasei MCC1849 (MCC1849)

Non-viable MCC1849 has not shown significant effects on immune parameters involved in the response to influenza vaccination in elderly people with immuno-senescence.[21]

6. Lactobacillus casei strain DN-114 001 (DN-114)

The administration of DN-114 reduced the incidence of acute diarrhea in healthy children aged 6–24 months. The incidence and frequency of diarrhea were significantly reduced by supplementation with DN-114 as compared with the control group. Another report says that DN-114 001 could reduce the incidence of common infectious diseases including diarrhea in children aged 3–6 years who were attending day care or school, although the detailed mechanism is still unclear.[22,23]

7. Lactobacillus plantarum L-137 (HK L-137)

The immune-modulatory effects of heat-killed HK L-137 were evaluated and the results showed that HK L-137 augmented the innate and acquired immune responses in mice and human subjects, particularly in view of the production of type 1 IFNs and interleukin (IL)-12. Assessment of the effects of HK L-137 intake for 12 weeks on URTI symptoms and immune functions in human subjects who were experiencing high levels of psychological stress showed thatThe incidence of URTIs was significantly lower in the HK L-137-treated group than in the control group. The percentage change from baseline of the concanavalin A-induced proliferation of peripheral blood mononuclear cells (PBMCs) was significantly greater in the HK L-137-treated group than in the control group, although serum IFN-β production was not significantly different between these groups.[24-26]

8. Enterococcus faecalis FK-23

The paraprobiotic FK-23 (Enterococcus faecalis strain FK-23) reduced alanine aminotransferase (ALT) levels in adult HCV-positive subjects but did not decrease viral load. They suggested that FK-23 might change the microbiota in HCV patients then it played a role in decrease in ALT level.[27]

9. Saccharomyces boulardii

Oral administration of Saccharomyces boulardii and rehydration significantly reduced duration of diarrhea in acute rotavirus gastroenteritis children in Bolivia, compared with control rehydration alone. Detailed mechanism is not available.[28]

10. Bifidobacterium animalis Bb12

Studies on Bifidobacterium animalis subspecies lactis (Bb12) on intestinal immunity and inflammation. (Anti-poliovirus-specific IgA and anti-rotavirus-specific IgA were assessed.) Bb12 significantly increased anti-poliovirus-specific IgA, but not anti-rotavirus-specific IgA, although it showed the tendency of increase.[29]

11. Bifidobacterium lactis B94

A study in Turkey, reported that Bifidobacterium lactis B94 with oral rehydration treatment significantly shortened diarrheal period in acute rotavirus gastroenteritis children (5 months to 5 years old), compared with control oral rehydration alone.[30]

12. Lactococcus lactis subsp. Lactis JCM 5805 (L. lactis JCM 5805)

Plasmacytoid dendritic cells (pDCs) play a crucial role in antiviral immunity through the production of large amounts of IFNs. L. lactis JCM5805 reported to activate human pDCs among PBMCs from healthy volunteers, especially in a subgroup of volunteers who originally showed a low pDCs activity, and it also significantly reduced cumulative common cold symptoms .The prophylactic effects of L. lactis JCM5805 on influenza-like illness in healthy volunteers during the winter season were reported based on the results of a double-blinded trial. The administration of 'L. lactis JCM5805' resulted in a significant decrease in the cumulative number of days of incidence of “cough” and “feverishness”, which were defined as the major symptoms of an influenza-like illness, as compared with the control group. Furthermore, when PBMCs from the volunteers treated with "L. lactis JCM 5805" were cultured with inactivated human influenza virus A/H1N1 (A/PR/8/34), the expression of IFN-α showed a higher tendency and that of interferon-stimulated gene 15 (ISG15) was significantly elevated as compared with the control group. These results suggest that "the intake of L. lactis JCM5805 can prevent the pathogenesis of an influenza-like illness via the enhancement of an IFN-α-mediated response to the influenza virus". In two separate studies, the expression of IFN-α and the mRNA level of ISG15 in PBMCs were significantly higher in groups treated with L. lactis JCM 5805 as compared to the corresponding control groups. In addition, the intake of yogurt containing L. lactis JCM 5805 significantly reduced the cumulative incidence rate of influenza among schoolchildren in a rural area of Japan. After 4 continuous weeks administration, L. lactis JCM 5805 significantly reduced cumulative days of symptom of sore throat, compared with control. In L. lactis JCM 5805 group, change in secretory IgA levels in saliva and phagocytic activity of neutrophil were significantly lower than those of initial level, but not in the placebo group. [31-33]

Mechanism of L. lactis JCM 5805-Mediated Inhibition of Viral Infections

A. Role of pDCs and Type 1 IFNs in Viral Infection

As dendritic cells (DCs) are the major immune cell subset that links the innate and acquired immune responses by recognizing pathogenic and endogenous inflammatory signals. Dendritic cells are subdivided into pDCs, myeloid DCs (mDCs), and CD8+ dendritic cells. Among these, "pDCs" are a rare and critical subset that acts as a “control tower” during viral infections.

To detect the presence of bacteria and viruses, pDCs utilize certain TLRs. Especially; they use TLR9 for the recognition of microbial nucleic acids via detecting unmethylated CpG motifs of DNA and TLR7 for the recognition of microbial RNA or synthetic guanosine analogs. The activation of pDCs by TLR ligand binding leads to the production of type 1 IFNs. The type 1 IFN family includes IFN-α and IFN-β, which serve as components of the first-line defense against infection by blocking viral replication. "The induction of type 1 IFNs is mostly associated with viral infections and it is well known that pathogenic bacteria stimulate IFN-α production". However, nonpathogenic bacteria including probiotics used in food preparation have been less intensively studied regarding their ability to stimulate DC-mediated IFNs induction. Screening of various lactic acid bacteria for their ability to stimulate IFN-α production by pDCs showed that L. lactis JCM 5805 was the most potent stimulator of type 1 IFN production.

B. Direct Activation of pDC by L. Lactis JCM 5805

The stimulatory effects of L. lactis JCM 5805 on type 1 IFNs production by pDCs and mDCs were evaluated .As a result of this direct activation of

DCs by L. lactis JCM 5805, the major type 1 and type 3 IFNs (i.e., IFN-α, -β, and -λ) were found to be induced efficiently. However, IFN-α production was completely abolished in dendritic cells obtained from TLR9 or MyD88 knockout mice. Thus, these data strongly suggested that "L. lactis JCM 5805 stimulated IFN-α production via TLR9/MyD88 signaling". Furthermore, the examination of whether IFN-α production was induced by CpG DNA, which is a known TLR9 agonist, or DNA extracted from L. lactis JCM 5805. Both CpG DNA and the DNA extracted from L. lactis JCM 5805 strongly induced IFN production. In addition, L. lactis JCM 5805 was observed to be specifically taken up by pDC, suggesting that its phagocytosis played an important role in activating pDCs and consequently inducing the production of IFNs.[34,35] IFN-α production by pDCs was synergistically elevated by L. lactis JCM 5805 treatment when they were co-cultured with mDCs. Therefore, cross-talk or direct contact between mDCs and pDCs was considered to be necessary for the effective induction of IFN-α production by L. lactis JCM 5805. In addition, L. lactis JCM 5805 stimulated the expression of immunoregulatory receptors such as ICOS-L and PD-L1 on pDCs and accordingly reinforced the induction of CD4+CD25+FoxP3+ regulatory T cells.[36]

C.The Mechanism of Action of L. Lactis JCM 5805 on the Immune System in Infectious Disease Models

When a lethal dose of parainfluenza virus (mPIV1) was inoculated intranasally to mice fed with L. lactis JCM5805, the survival rate was significantly higher than that of the control group (69% survival in L. lactis JCM 5805 and 0% survival in the control group on day 15 after inoculation). In the intestinal pDCs from the mice treated with L. lactis JCM 5805, type 1 IFN expression was significantly elevated, while a remarkable preventive effect against the infiltration of neutrophils into the lung tissue was observed. A significant increase in the expression of genes with antiviral activities including IFN-inducible mRNAs such as Isg15, Oasl2 (2'-5' oligoadenylate synthetase-like 2), and Rsad2 (radical S-adenosyl methionine domain containing 2) was observed upon treatment with L. lactis JCM 5805. Although lung is distantly located from the contact site (intestinal Peyer's patches) and L. lactis JCM 5805 cannot stimulate local pDCs in the lung directly, oral L. lactis JCM 5805 treatment resulted in a strong resistance against parainfluenza virus infection in vivo.[37]

As is well known, IFN-α plays an important role in the antiviral immune response by inducing the cytotoxic activity of NK cells, which contributes to the host defense against viral infections. Reports that L. lactis JCM5805 activated NK cells both in vitro and in vivo. Furthermore, the effect of L. lactis JCM5805 on NK cells was dependent upon the activity of dendritic cells. Among a number of activation factors for NK cells including IFN-α, IL-2, IL-15, and IL-18, IFN-α is regarded as one of the most efficient NK cell activation factors. In addition, it was reported that IFN-α production by virus-stimulated pDCs markedly increased the cytotoxic activity of NK cells .Possible mechanism for the antiviral effects of L. lactis JCM 5805 via activation of plasmacytoid dendritic cells (pDCs). It can noted the direct activation of pDCs by L. lactis JCM 5805 as the most plausible mechanism for the inhibition of viral infection, other underlying mechanisms have not been ruled out. Another report says that specific probiotic bacteria could bind and inactivate rotaviruses. Besides this direct interaction with viruses, it is also possible that L. lactis JCM 5805 competes for viral receptors on the surface of target cells, produces antimicrobial and potentially antiviral substances, and stimulates host-cell immune defense systems. Thus, in the future, it is necessary to test whether L. lactis JCM 5805 can also directly bind and inactivate viruses, since the resulting data could provide a basis for novel approaches to inactivate viruses and reduce the risk of mucosa-associated viral infections.

To detect the presence of bacteria and viruses, pDCs utilize certain Toll-like receptor (TLR) families. Especially, they use TLR9 for the recognition of microbial nucleic acids by detecting unmethylated CpG motifs of DNA and TLR7 for the recognition of microbial RNA or synthetic guanosine analogs. The activation of pDCs by ligand binding to TLRs leads to the production of type 1 IFNs. L. lactis JCM 5805 was specifically taken up by pDCs and its DNA extracts strongly induced IFN production. These observations suggest that the phagocytosis of L. lactis JCM 5805 by pDCs plays an important role in activating pDCs and stimulating IFN production via TLR9/MyD88 signaling.[38-43] IFN-α plays an important role in mediating the antiviral immune response by inducing the cytotoxic activity of natural killer cells, which contributes to the host resistance against viral infection.

CONCLUSION

We described the efficacy of probiotics for the prevention or treatment of infectious diseases. Although the benefits of vaccines and antiviral drugs for the prevention and treatment of viral diseases are obvious, their effectiveness is hindered by the large number of viral species and their subtypes as well as the high mutation rate of viruses. Since viruses mutate constantly and produce a serologically diverse viral population, it is challenging to establish an effective means of protecting humans from viral infections. There have been several clinical reports regarding the use of probiotics for the prophylaxis or treatment of infectious diseases. Such agents are considered to be safe, affordable and easy to consume because of their long history of use in foods. The state of knowledge regarding the immune-modulatory 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, has been widely studied.

In this review, we discussed the anti-influenza activity of L. lactis JCM 5805, which has the potency to directly stimulate pDCs via TLR9 and thereby promote viral control. Although further detailed research is necessary, probiotics are expected to be among the rational adjunctive options for the treatment and prophylaxis of viral infections.

The patho-physiology of COVID-19 clearly indicate the sensitivity of SARS CoV-2 to IFN. The Cuban republic studies on treatment of COVID-19 patients with IFN shows positive results. Considering the proven antiviral and immune-modulatory activity of Probiotics and ablity to stimulate Interferon production, it is recommended to use probiotics as the adjunctive therapy for the prophylaxis of COVID-19. It is also recommended to add probiotics (like in the form of yogurt, curd *etc.*) in the daily diet to develop resistance against viral infections.

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