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ORIGINAL CONTRIBUTION

Effects of Probiotics on Viral infection-a Review

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ABSTRACT

Due to its offhand use of chemical drugs, antimicrobial resistance against pathogenic bacteria is increasing day by day. Not only bacteria but virus is also showing step by step resistance against anti viral drugs either it's older or the newer one.Over the years, beneficial strains of lactic acid bacteria (commonly popular as Probiotics) have been successfully used to treat gastrointestinal, oral, and vaginal infections caused by pathogenic microbes. Some recent studies shows that this group of bacteria along with some beneficial strains of yeast can be successfully employed to stop and reduce symptoms of infections caused by common viruses, especially tract viruses, but also for viral digestive infections (such as rotavirus, coronavirus, or norovirus) and other viral infections (such as viruses that cause hepatitis, human papillomavirus, human immunodeficiency virus, and herpes simplex virus).Ongoing continuous research on developing vaccines and antiviral agents against various viral infections, no specific treatment or vaccine has been approved for several enteric or respiratory viral infections; In addition, the efficiency of currently available treatments remains limited. One of the foremost reliable and recommended strategies to regulate viral infections is prevention. Recently, intense studies are going on that specialize in a promising approach for treating/preventing various viral infections using probiotics.In this review, we emphasize the protective effects of probiotics against viral infections and proposed mechanisms for suggestion of a completely unique and costeffective treatment against current and newly discovered viruses like SARSCoV2 and other viruses.

KEY WORDS: Antiviral, Probiotics, SARSCoV2, Immunomodulatory activity

1. INTRODUCTION

"Probiotics" are microorganisms which promote other beneficial microbial growth was coined in 1965 by Lilly and Stillwell [1]. As per FAO/WHO probiotics are "live microorganisms which, when administered in adequate amount, confer a health benefit to the host" [2]. To be classified as a probiotic, the microorganism should have certain characteristics, such as having a human origin source, being non-pathogenic, being resistant to the intestinal environment, and having a beneficial effect on the immune system. The majority of the probiotic microorganisms are 'generally recognized as safe, GRAS' [3]. Most of the probiotics marketed till date for human consumption are from Lactic acid bacteria (LAB) group. LAB is the Gram positive, non sporulating lactic acid forming bacterial group that includes*Lactobacillus*, *Lactococcus*, *Pediococcus*, *Enterococcus* and other species. Over the years researchers have been found huge antibacterial and antifungal activities of this group. They have been successfully used in the treatment of some skin infections, Irritable Bowel Syndrome (IBS), Diarrhea also in oral and vaginal infections. Some of them exhibit cholesterol lowering activity, antitumor activity and immunomodulating characteristics. Though little attention has been given to the antiviral capabilities of probiotics, in some recent studies,

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antiviral activities have been reported for probiotic bacteria and/or their metabolites[4, 5].

The relationship among beneficial bacteria, pathogenic viruses and host immune system is very complicated. Normally a virus entered into the body has to face two layers of immunity provided by the host immune system, innate and adaptive immunity. If overcome these barriers they can infect various organs and tissues of a human, like in Polio the Poliovirus attacks the spinal cord, in diarrhea the Rotavirus infect the colon of a child, in Hepatitis B infection the virus infect the liver, in HIV the infection is found in WBC, in Influenza lungs and respiratory tract gets affected, the Measles virus infects the respiratory tract, then spreads throughout the body and so on. According to Sundaraman *et al*., 2020 [6] probiotics have both the direct and indirect influence over the viral infection. They can directly prevent the viral attachment to host cells [7, 8]interact with virus[9] secreteantiviral metabolites in the form of exopolysaccharides (EPSs) [10], or other antiviral antimicrobial peptides (AMPs) [11, 12]); bacteriocins, or by indirectly modulatingthe mucus layer [13, 14] and via stimulation of immune system.

2.1 PREVENTION OF ENTRY: DIRECT INTERACTION BETWEEN PROBIOTICS AND VIRUS

The first step in viral infection is attachment to specific host or target cell. Probiotics can compete with the virions for the same specific attachment site or they can capture the virions directly. Some strains of *Lactobacillus* and *Bifidobacterium* can prevent *Vesicular Stomatitis Virus* (VSV) by directly binding to their cell surface and can reduce viral infectivity up to 60%. [7]. Wang *et al*, 2013[15] showed the inhibitory potential of the probiotic *Enterococcus faecium* NCIMB 10415 on the replication of two porcine strains of influenza virus (H1N1 and H3N2 strain) in a continuous porcine macrophage cell line and the result showed an inhibition of virus multiplication by up to four log units in the *E. faecium* treated cell.Another study of 2013 showed that binding of CD4+ receptor present on the outer surface of *Lactobacillus* species with HIV virus prevents the attachment of HIV virus to CD4+ cells of immune system [8]. One of the recent studies[16] showed the probiotics have the ability to inhibit the enveloped viruses such as herpes simplex type 2 (HSV-2) by entrapment.

2.2 RELEASE OF DIFFERENT ANTIVIRAL COMPONENT

As a normal inhabitant of human body, Lactic acid bacteria and their metabolites exert an important role in innate immunity. Lactic acid, acetic acid, formic acid produced during carbohydrate fermentation process reduces the pH below 4 and at this lower pH most of the pathogenic organisms including human immunodeficiency virus type 1 (HIV-1) and HSV-2 get inactivated [17, 18, 19].Metabolite hydrogen per oxide also can inhibit the replication of new virions within the host. As LAB are catalase negative, when grown in presence of oxygen, they accumulate H_2O_2, hydroxyl radical, superoxide in higher concentration within the cell. In recent studies these reactive components showed antiviral properties against type-1 and type-2 HIV, Influenza, HSV etc. [17, 20]Exopolysaccharides (EPS) extracted from probiotic *Lactobacillus plantarum* strain N4(Lp) also shows antiviral activities against the Transmissible Gastroenteritis Virus (TGEV) which causes severe diarrhea and other symptoms and ultimately end up in death in young piglets [21]. EPS derived from some other probiotics showed immuno-modulatory activities. EPS26a from *Lactobacillus* sp. inhibits the replication process of human adenovirus type 5 (HAdV-5). EPS derived from *Bacillus licheniformis* strain T14 can prevent HSV-2 infection at 300 and 400 $\mu g \cdot mL^{-1}$ in human peripheral blood mononuclear cells (PBMC). *Lactobacillus delbrueckii* OLL1073R-1 secretes an EPS which interferes with the components of innate immune response like the Toll-like receptor 3 (TLR3) and the expression of interferon (IFN)-α, IFN-β, MxA, and RNase L in porcine intestinal epithelial (PIE) cells.[22].In a related study by Mastromarino *et al.*, 2011, it has been found that theinhibitory antiviral activity of *Lactobacillus brevis* towards HSV-2 is likely due to a heat-

resistant non-protein cell surface bacterial component.[23]

Among the proteinaceous antimicrobial proteins (AMPs), bacteriocin is well studied from different bacterial sources and it has probiotic application also. Bacteriocins are ribosomally synthesized small peptides, with antibacterial as well as antifungal activities. Some recent studiesshow how this small peptide can prevent viral growth within host tissues. Before viral entry into human cells they can block viral receptors or they can interfere with viral replication after entry. As for example Duramycin, a peptide bacteriocin produced by Streptomycetes, binds phosphatidylethanolamine in enveloped virions and blocks the receptor TIM1 for Zika virus and as a result infection in placental cells and explants reduced many fold [24]. The study of Serkedjieva *et al*., 2000 showed different mode of action of bacteriocin from *Lactobacillus delbrueckii* against Influenza virus [25]. A 5kDa bacteriocin of *Lactobacillus delbrueckii* reduced virus-induced cytopathic effect, infectious virus yield, expression of viral protein at outer surface of infected cells etc. Antiviral activity by enterocin CRL35 and ST4V has been observed against HSV-1 and HSV-2 in Vero and BHK-21 cells, affecting intracellular viral multiplication, and inhibiting late stages of replication [26–28]. Similar result was observed from a *Bacillus* originated bacteriocin subtilosin,which affects late infectious stages of both HSV type 1 [11] and HSV type 2 [12].

2.3 STIMULATION OF IMMUNE SYSTEM

The components of human innate immune system like epithelial cell surfaces, toll like receptors (TLR), some anti-microbial protein like defensin, natural killer (NK) cells, phagocytic cells continually roam throughout the body and search for external foreign objects including viruses. Plasmacytoid dendritic cells (pDC) are specialized immune cells that recognize both viruses and bacteria, and they play an important role in inducing the cytotoxic activity of NK cells via the production of interferon-alpha (IFN-a) - interferons are cytokines that inhibit viral replication by interfering with the transcription of viral nucleic acid.[22]. Recent studies show that Probiotics generally enhance the number and activity of NK cells against the infecting viruses [29, 30]. Some probiotics can influence the adaptive immunity also. This type of immunity is very specific, appeared after 2-3 days later of the infection and generally mediated by B cells and T-cells of types T_H (CD4, helper) and T_C (CD8, cytotoxic). One of the important features of this type of immunity is presence of long term pathogen specific memory cells which help in host cells protection during further attack of the same pathogen. Wang Y. *et al*., (2017) observed that the probiotic strain *L. rhamnosus* GG (ATCC53103) produces the soluble factor Msp2 (or p40) protein, which signals epithelial cells in the gut to stimulate B-cells and produceg IgA antibodies [31]. *L. plantarum* strain YU, isolated from food products, showed high interleukin 12-inducing activity in mouse peritoneal macrophages. They have enhanced natural killer cell activity in spleen cells and produce IgA from Peyer's patch cells. [32]

2.4 MODULATION OF THE MUCUS LAYER

The internal organ system of human body is covered with a wet biopolymer matrix called mucus. Whenever a bacterial or viral pathogen wants entry to organ system this mucosal epithelium layer is the vital barrier they have to cross over. Body's normal microflora remains attached to these epithelial cells of lungs, vagina and gastro-intestinal tract and prevent the entry of pathogens. They compete with the pathogens for attachment site, nutrition and also induce expression of some antimicrobial proteins likemucin 2. Porcine gastric mucins have been shown to prevent infection of epithelial cells by a variety of viruses including human papilloma virus type 16, Merkel cell polyoma-virus and a strain of influenza A virus [13]. Another study by Nunn *et al*., (2015)showed direct formation a barricade like structure by some probiotic bacteria which prevents the entry of HIV-1 through cervicovaginal mucus (CVM) [33].Again combination of probiotics like*Bifidobacterium* and *Lactobacillus* species

and prebiotics like inulin reduced the severity of rotavirus diarrhea several fold [34].

3. EFFECT OF PROBIOTICS ON RESPIRATORY TRACT INFECTION (RTI) WITH SPECIAL EMPHASIS ON COVID-19:

One of the major causes of respiratory tract infection is viral pathogens. These include rhinovirus, respiratory syncytial virus, influenza virus, human parainfluenza virus, human metapneumovirus, measles, mumps, adenovirus, and coronavirus [35]. They can infect both upper respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) and according to Van Riel *et al*., 2006, lower respiratory tract infections are more severe and important than upper respiratory tractinfections [36]. The newly emerging virus during 2019, theSARSCoV-2(Covid 19) can attack both the tract and shows common symptoms such as high fever, flu, sore throat, headache, runny or blocked nose, weakness, muscle pain, and diarrhea similar like the common respiratory tract infecting Influenza virus. It also showed some other symptoms like loss of smell or taste or both, pneumonia, acute respiratory distress syndrome (ARDS) and lastly multiple organ failure and death. In recent days probiotics are used for controlling different diseases of GI tract, respiratory system and also to modulate the local and systemic immune response. Most of the respiratory tract infection occur due to imbalance in the the normal microbial population attached to mucosal epithelium of gut and respiratory system. The Mucosal Associated Lymphoid Tissue (MALT) plays an important role in promoting the immune response of the respiratory, digestive, and urogenital tracts. But due to this imbalance, several bacterial as well as viral infections may occur to these organs including RTI. In one of the study by Abt *et al*., (2012), it has been observed that the gut microbiome can control these RTI by inducing immune responses at distant mucosal sites like the lungs.As probiotics can't be administered directly to respiratory system, majority of probiotics can inhibit the respiratory viruses by immunomodulatory mechanisms [38]and also through gut. This type of immune modulation helps patients showing cytokine storm due to COVID 19 attack. There are several evidences that showed the probiotic strains has the ability to modify the dynamic balance between proinflammatory and immunoregulatory cytokines that allow reduction in viral load without causing damage to the lungs. Oral administration *Bifidobacterium longum*BB536for continuous 2 weeks before infection of Influenza virus showed an anti-IFV A/PR/8/34 (H1N1) activity in BALB/c mice and this is due to reduction in proinfl ammatory cytokines concentration, such as IFNγ and IL-6 [39]. This helps to prevent ARDS, one of the major complication of COVID-19 infection. Studies showed suppression of plasma pro-inflammatory cytokines (IFN-γ, TNF-α) in middle-aged adults in presence of *Lactobacillus plantarum* DR7 and enhancement of anti-inflammatory cytokines (IL-4, IL-10) in young adults, along with reduced plasma peroxidation and oxidative stress levels [40]. Administration of certain bifidobacteria or lactobacilli has beneficial impact on influenza virus clearance from the respiratory tract [41]. A recent study in mice has shown that oral administration of Lactobacillus acidophilus CMCC878, started 24 h after pulmonary inoculation of *Pseudomonas aeruginosa* and *Staphylococcus aureus* reduced bacterial load in the lungs, and decreased lung damage and systemic inflammation [42].

4. CONCLUSIONS

Probiotics are generally safe for all the ages from infant to older persons. They exhibit direct and indirect mechanisms to eradicate viruses from human body (both internal and external organs). Most of the applications and studies on probiotics are confined to the gastrointestinal tract but they can also be applied to other organ system effectively. Several LAB strains have been considered for pharmaceutical applications after a number of clinical studies and human trials (placebo-controlled, double-blind, randomized trials). From recent clinical and experimental studies several evidences showing antiviral activity of probiotic strains against influenza, rhinovirus, and respiratory syncytial virus are emerging [43]. Though reports are available for other coronavirus strains [44], the

effect of probiotics still not tested against the new SARS-CoV-2 virus. With vaccination and other supportive measures may be this approach will help us to conquer this pandemic.

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