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Possible anti-inflammatory role of Probiotics in the treatment of Covid-19 disease

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Abstract

Covid-19 is a viral disease that has recently become extremely dangerous and lethal. A severe inflammatory response develops as a result of the viral disease affecting the body. According to some research, the development of this response causes damage to various organs and tissues. Natural compounds may reduce or prevent the potential damage to the organism caused by this inflammatory response. Probiotics have powerful anti-inflammatory properties, according to new research. As a result, the potential anti-inflammatory effects of probiotics in Covid-19 disease will be discussed in this study.

Keywords: anti-inflammatory, probiotics, covid-19

Introduction

One of the contentious issues is Covid-19 (SARS-CoV-2) disease, which causes acute respiratory syndrome and is found all over the world (1). The clinical symptoms of this disease, fatigue, headache, diarrhea, cough, fever, and shortness of breath, appear after a 5-7 day incubation period (2). Respiratory failure, acute respiratory distress syndrome (ARDS), or multiple organ failure may occur in some patients. In the majority of cases, it is asymptomatic or mild (1, 3). Infection with COVID-19 can result in COPD, coagulation dysfunction, septic shock, metabolic acidosis, cardiac arrhythmia, heart failure, liver dysfunction, kidney damage, or secondary infections (2).

Many studies have found that inflammation is a natural defense mechanism against a variety of pathogens and that it is linked to oxidative stress in a variety of pathological conditions (4-12). In Covid-19 patients, there is substantial evidence that systemic hyperinflammation contributes to lung and multi-organ failure (1). Ferritin, fibrinogen, D-dimer, interleukin-6 (IL-6), C-reactive protein, and procalcitonin levels were found to be elevated in Covid-19 patients' sera. These clinical and laboratory findings

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are linked to macrophage activation syndrome and hyperinflammation (3).

Macrophages and monocytes play critical roles in the inflammatory responses associated with severe Covid-19 infection (13). TNF-, IL-1, IL-6, and IL-8 are proinflammatory cytokines secreted by these immune cells. In critically ill patients, Covid-19 (14-17) was discovered. In Covid-19 disease, excessive cytokine release causes acute heart damage, acute respiratory failure, or the development of multi-organ failure and worsening of the condition (2). As a result, using anti-inflammatory agents in the treatment of Covid-19 disease is critical in reducing disease severity. Identifying new pandemic-fighting agents in addition to existing ones will aid in the development of new pandemic-fighting strategies (1). Probiotics could be used instead of these new agents. Probiotics are living microorganisms that have been shown in numerous studies to suppress inflammation and protect tissue from the effects of inflammation (14-17). The purpose of this study, according to this information, is to explain the effect of probiotic use in addition to existing agents in the treatment of covid-19-induced inflammation.

Virus morphology and way of attachment to the cell: The Coronavirus is a single-stranded (+) RNA-enclosed virus, according to its morphological structure. Scientists in the United States and the United Kingdom identified this virus as the cause of the common cold in humans in the 1960s (18). Coronaviruses have a diameter of 80-120 nm and can be pleomorphic or spherical. Photos taken with an electron microscope in 1968 revealed that this virus family has characteristics similar to the "solar corona," which gets its name from the Latin word "coronavirus" (19).

The coronavirus structure has been determined to be made up of four primary structural proteins. Among these proteins are: S is a trimeric Spike glycoprotein found on the surface of the viral envelope that is required for viral entry into cells. The second protein is known as matrix or membrane protein M. The third protein, E, is a small envelope protein that is required for virus collection and release. The fourth protein, N, is known as the nucleocapsid protein. It helically attaches to the RNA genome to form the symmetrical nucleocapsid (Figure 1). (20).

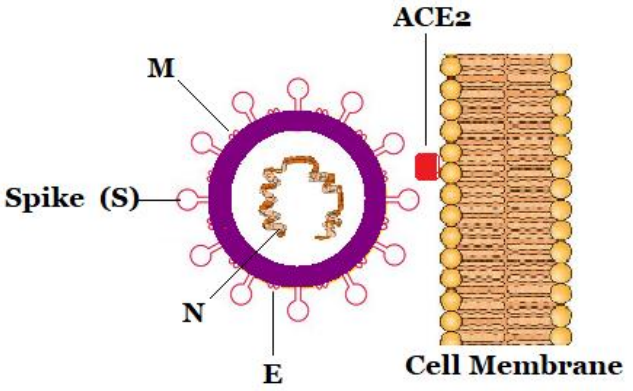

Figure 1. The structure of the coronavirus and its entry point into the cell. S is an abbreviation for the trimeric Spike glycoprotein. It binds to the ACE2 receptor on the cell membrane. M denotes membrane or matrix protein, and E denotes small envelope protein.

Despite a few critical amino acid differences, homology modeling revealed that the new virus had a receptor binding domain structure (RBD) similar to SARS-CoV. It was thought that the virus entered cells through the Angiotensin Receptor Enzyme-2 (ACE2) protein, which is abundant in the kidney, heart, lung, testis, and gastrointestinal tract (21). The membrane-bound protein ACE2 is responsible for converting Ang II into Ang 1-7. (22). The Covid-19 infection cycle includes several steps: These are the steps. 1. Find and attach to the cell's receptor (s). The second modification affects the S protein's structure and proteolysis. Fusion with the cellular membrane is the third step. The fourth step is for the virus to enter host cells via endocytosis (23).

The virus uses an innate biological process to replicate viral RNA in host cells. The spiky glycoprotein S found on the surface of the viral phospholipidic membrane is well known to play an important role in coronavirus pathogenesis and infection. The RBD of the S protein

interacts with the ACE2 receptor in cells to initiate the SARS-CoV-2 life cycle (24, 25). Figure 1.

The Covid-19 is experiencing a cytokine storm: The cytokine storm that develops as a result of Covid-19's inflammatory response may be linked to clinical deterioration and an increased risk of death (26). In Covid-19 patients, blood levels of cytokines such as monocyte chemo attractant protein 1 (MCP1), interferon-alpha (IFN-), IL-1ß, interferon-gamma (IFN-), and induced protein 10 (IP10) increased (27). Furthermore, IL-10, IL-7, IL-2, macrophage inflammatory protein 1-, IP10, granulocyte colony-stimulating factor (G-CSF), MCP1, and TNF- levels were found to be quite high in severe Covid-19 patients (27). It was discovered that those who died from severe Covid-19 disease had extremely high IL-6 levels (28).

This highlights the significance of cytokines in the severe Covid-19 course. A cytokine storm was divided into two stages in one study (29). The first stage is the absence of immunity. The secondary stage is distinguished by a hyperactive immune response, which appears to be a clinical manifestation of a cytokine storm (30). Coronavirus causes delayed secretion of type I and III IFNs, including IFN-/ß, in the early stage and excessive secretion of pro-inflammatory cytokines from mononuclear macrophages in the later stage, according to experiments (31). Low IFN activity and IFN-induced gene down-regulation have been shown to impair type 1 IFN responses as well as hyper-inflammatory responses involving IL-6 and TNF- (32-37).

Probiotic effect on immune responses: Probiotics are living microorganisms that contain a variety of bacteria and yeast strains and have beneficial effects on the host when used appropriately. Probiotic bacteria include *Lactobacillus, Bifidobacterium, Leuconostoc, Pediococcus,* and *Enterococcus* (38). In the intestine, probiotics regulate, stimulate, and modulate a wide range of functions, including digestion, metabolism, congenital epithelial immunity, pathogen competitive exclusion, and brain-intestinal communication (39, 40). Intestinal microorganisms produce non-toxic metabolites that play important roles (41-43). Probiotics fulfill three roles: metabolic, protective, and trophic (44). Probiotics generate energy by fermenting indigestible foods known as prebiotics and have significant anti-pathogenicity, anti-obesity, antidiabetic, anti-inflammatory, anticancer, and angiogenic properties, as well as effects on the brain and central nervous system (45).

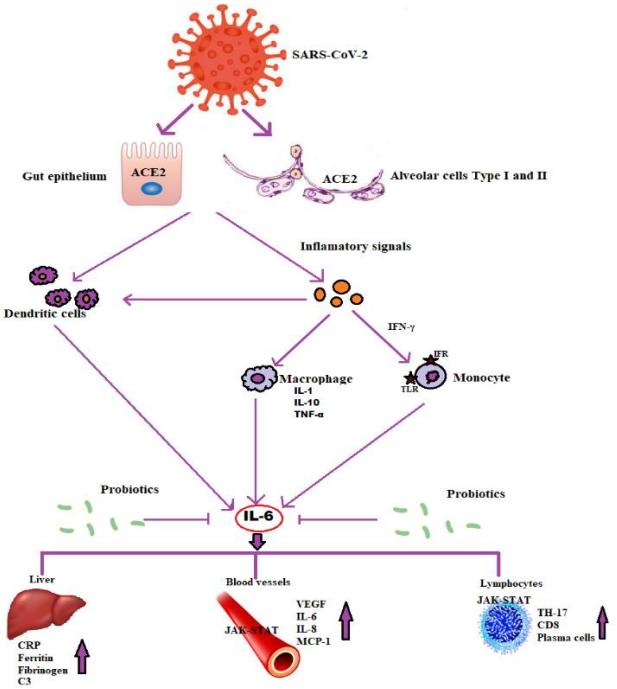

Figure 2. Covid-19 is in the grip of a cytokine storm. Probiotics have anti-inflammatory properties. TNF- stands for tumor necrosis factor alpha; IFN stands for interferon; IL stands for interleukin; and JAK/STAT stands for Janus kinase-signal transducer and activator of transcription. CD8 is an abbreviation for cluster of differentiation 8, TH-17 is an abbreviation for T helper 17, and VEGF is an abbreviation for Vascular endothelial growth factor. MCP-1 is an abbreviation for monocyte chemoattractant protein-1, and CRP is an abbreviation for C-reactive protein. C3 is an abbreviation for complement component 3, ACE2 is an abbreviation for angiotensin-converting enzyme 2, TLR is an abbreviation for toll-like receptor, and IFR is an abbreviation for interferon.

Probiotics have been shown to influence humoral, cellular, and nonspecific immunity, as well as the

immunological barrier (46, 47). In vivo, probiotics have been shown to increase peripheral immunoglobin production, stimulate IgA secretion, and inhibit pro-inflammatory cytokine production (48). Activated intestinal epithelial cells express a variety of antigen-presenting and costimulatory molecules. Furthermore, as both CD4+ and CD8+ cells, these cells contribute to the activation and expansion of regulatory T-cells (Tregs). Proteasomes are involved in the breakdown of endogenous and exogenous proteins for MHC class 1 and 2 antigen presentation (49). Probiotic bacteria regulate epithelial cell proteasomal activity and may be involved in the mechanism of epithelial-derived T cell activation in the intestine (50, 51).

Because of their biological activities and inhibitory properties against pathogenic microbes in the host, probiotics have been shown to produce non-toxic and non-pathogenic non-viable metabolic byproducts that are resistant to mammalian enzyme systems, such as bacteriocins, organic acids, acetaldehydes, diacetyl, ethanol, and hydrogen peroxide, and can be used as an alternative to antibiotics (52, 53). According to some studies, probiotics boost antioxidant production (glutathione) and reduce oxidative stress. Probiotic microorganisms, such as L.acidophilus NCDC14 and L.casei NCDC19, inhibit lipid peroxidation and reduce STZ-induced oxidative damage in rat pancreatic tissues (54).

Lactobacillus rhamnosus GG, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium lactis, and Streptococcus thermophiles all inhibit mononuclear cell proliferation (55). Several studies have revealed basic molecular mechanisms of probiotics, including IgA secretion, cytokine production, antibacterial agent production, tight junction strengthening against intercellular bacterial invasion, and competition for enterocyte adhesion with new pathogenic microorganisms. The immunomodulatory effect of probiotics is attributed to the release of cytokines such as interleukins (ILs), tumor necrosis factors (TNFs), interferons (IFNs), transforming growth factor (TGF), and chemokines from immune cells such as lymphocytes, granulocytes, and macrophages (56).

Probiotic strains influence the gut barrier by inducing IgA production in B cells. In vitro, probiotics have been shown to influence cytokine production by APCs, which initiate adaptive responses in enterocyte cells (HT 29, caco-2, and dendritic cells derived from PBMC). Cytokines also aid in the immune system's defense against bacterial, fungal, viral, and other pathogenic components. The inflammatory process is caused by pro-inflammatory and anti-inflammatory cytokines. Interleukin-10 (IL-10) is an anti-inflammatory cytokine produced by monocytes, T cells, B cells, macrophages, natural killer cells, and dendritic cells. Immunostimulatory probiotics combat inflammation and cancer cells by increasing IL-12 production, which activates NK cells and promotes Th1 cell proliferation. Probiotics can also help with allergies by balancing the Th1 and Th2 immune systems. Immunomodulatory probiotics, on the other hand, have been shown to reduce allergies, inflammatory responses, and IBD by increasing the production of IL-10 and Treg cells (57). Anti-inflammatory properties are found in probiotics. Probiotics increase IL-10 while decreasing IL-12. (58). Probiotics either activate the immune system by increasing IL-12, IL-1, and TNF- levels, or they act as an anti-inflammatory by increasing IL-10 and TGF- levels (59). T helper cells play a role in immune responses. Th1/Th17 cells produce proinflammatory cytokines such as IL-12, IFN-, IL-6, and IL-17. Th2 cells produce cytokines like IL-4, IL-5, and IL-13.

Treg cells suppress T cell functions such as Th1, Th2, and Th17. L. plantarum and B. infantis can be reduced to IFN- and IL-10 levels (60, 61). Probiotic mixtures can also reduce the production of proinflammatory cytokines like IL-17, IFN-, and TNF- while increasing IL-10 and/or Treg cells (62). In vivo studies on mice that do not contain microorganisms, for example, have

shown that morbidity increases during acute lung infection (63). Another study discovered a link between the severity of Mycobacterium tuberculosis infections in the lung and the intestinal microbiota (64). Furthermore, as a result of previous research, we discovered that probiotic application suppressed the increase in TNF-, IL-6, IL-8, and IL-1, which increased as a result of inflammation caused by various toxic agents in rats (14-17).

CONCLUSION

As a result, a more effective treatment method for the highly contagious and lethal coronavirus epidemic has yet to be discovered. This situation motivates researchers to seek alternatives to human coronavirus infections. According to various studies, probiotics play an important role in reducing inflammation in various tissues. Coronavirus has been shown to cause severe inflammation and death after tissue damage in a variety of tissues. In this context, we believe that the probiotics mentioned can be used as an alternative to the current anti-coronavirus agents.

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