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Promising Indicators in Probiotic-recommendations in COVID-19 and its Accompanying Diseases

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Abstract

Scientific data suggests the possible beneficial role of probiotics in treatments for COVID-19, but the species/strains-specificity and disease-specificity of probiotics need high attention in choosing the appropriate probiotic in diseases, in particularly in the COVID-19. We hope this review will raise awareness of the COVID-19 probiotic recommendations, highlighting the latest scientific information about virus/hydrogen peroxide/probiotics and the importance of finding out of a specific "criterion" for the probiotics' recommendation in this disease.

Introduction

Literature data indicate an association between COVID-19 severity and diabetes [1], [2]. Most COVID-19 patients are prone to impaired glucose metabolism; glycemic testing and control are important even if the patients have no pre-existing diabetes [3]. Furthermore, hypertension [1], [4], acute coronary syndrome [5], rheumatic [6], gastrointestinal [7], and neurologic features [8], [9] in SARS-CoV-2 infection have been reported. Potential associations between host blood characteristics and gut bacteria [10], [11], [12], as well as between gut microbiota and COVID-19 – accompanying diseases have been actively discussed [13]. Sever childhood respiratory illness in association with vitamin D deficiency has also been shown [14]. The clinical trials and experimental studies on COVID-19 treatments are ongoing worldwide, increasing the obtained information on infected people, blood and organ system, genomics, and metabolomics. Despite of a safe and efficacious vaccines, respiratory tract infections will remain of concern for high morbidity and mortality rates among the elderly due to low level vaccine-induced immune response [15], [16]. Recently collected data appear to confirm the possible beneficial role of probiotics in treating COVID-19 patients [17], [18]; however, there is insufficient scientific evidence specific to COVID-19. Therefore, species/strain- and disease-specificity of probiotics need more attention [19]. Probiotics may have beneficial, harmful, or neutral impact on the host. For example, in an *in vivo* study of their radio-preventive/protective characteristics, 17 putative probiotic lactobacilli, including the strain *Lactobacillus acidophilus* DDS®-1 (from Lacto-G, a marketed symbiotic formulation), the commercial probiotic product Narine (*L. acidophilus* INMIA 9602 Er-2

strain 317/402), and several strains of *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus fermentum*, *Lactobacillus delbrueckii*, and *Lactobacillus helveticus*, have shown varying impact on 4.5 Gy, whole-body X-ray irradiated rats before and after the irradiation [20]. In addition, since COVID-19 patients may rapidly "transform" their physiological state following an infection by the virus, potential probiotic-effects and the individual dietary, nutritional, medical, lifestyle, and environmental risks should be carefully investigated before any recommendation. Since it was recognized that the SARS-CoV-2 pandemic has been particularly deadly in older adults [21], [22], we hope to raise awareness about probiotics for COVID-19 patients and highlight the possible importance of hydrogen peroxide production for any probiotics recommendation in this disease.

Probiotics/Immunobiotics

Nowadays, the interaction of probiotics with the SARS-CoV-2 spike (S) proteins [22] and with the gut microbiome [23], [24], [25] is at the attention of the researchers. In general, the benefit of probiotics is determined by the complex interactions between probiotic bacteria, the host intestinal microbiota, and the gut epithelium [23], [24], [25]. Frequently, probiotic lactobacilli are able to (i) promote the expression and regulation of tight junctions and adherence junctions, resulting in the restoration of a defective epithelial barrier and (ii) interact with immune cells through pattern recognition receptors, such as Toll-like receptors, which on activation stimulate or suppress various immune responses [26], emphasizing host gut-blood [27], and gut-brain [28] linkages. Probiotic immunobiotics beneficially regulate the mucosal immune system [29] and have valuable antagonistic potential against nosocomial pathogens. Among the many proposed mechanisms by which immunobiotics mediate their effects is the modulation of the innate immune response both by anti-inflammatory [30], [31] and pro-inflammatory effects [32]. In addition, immunobiotics have been shown to enhance the adaptive immune response, for example, antibody formation [33]. Inhibition of adherence, attaching, and effacing microorganisms [34], modulation of mucosal barrier function [35], or inhibition of trophil migration [36] may also be important mechanisms, whereby immunobiotics may influence intestinal diseases [37]. There is also strong evidence that signaling molecules/determinants are preserved in immunobiotic strains [38], and certain immunogenic strains enhance immune function, especially in subjects with less than adequate immune response [39].

Human Viral Diseases, Oxidative Stress, Hydrogen Peroxide, and Probiotics

The prevalence of chronic diseases increases with age. Increased production of reactive oxygen species is involved in the pathogenesis of cardiovascular diseases, such as coronary atherosclerosis, hypertension, diabetic vascular complications, and heart failure [40]. These are also known risks for potentially worse COVID-19 outcome. The patients with severe COVID-19 history have also often been found to have elevated D-dimer, troponin, ferritin, C-reactive protein, and alanine aminotransferase [41], and circulating endothelial cell levels [42], as well as vitamin D deficiency [14]. It seems that there is a link between oxidative stress and a variety of pathological conditions, including COVID-19 [43] and its accompanying diseases, such as diabetes [44], hypertension [45], acute coronary syndrome [46], rheumatic [47], gastrointestinal [48], or neurologic features [49].

Both enzymatic and non-enzymatic pathways are involved in endogenous antioxidant defense mechanisms. The enzymes superoxide dismutase, catalase, the prosthetic group Se-containing glutathione peroxidase, and glutathione reductase are common antioxidants; important in endogenous antioxidant defense systems [44]. Iron is an essential element for virtually all cell types due to its role in energy metabolism, but free iron may induce cellular and organ damage through the free radicals [50]. Peroxidase uses various organic compounds: Polyphenols, aromatic amines, ascorbic acid, etc., to destroy hydrogen peroxide and organic peroxides (oxygen donors), and to form a high valent iron intermediate named Compound I. In erythrocytes and some other tissues, glutathione peroxidase protects membranes and hemoglobin from oxidation by peroxides. Peroxisomes, the cell organelles known as important centers in innate immune-, lipid-, inflammatory-, and redox-signaling networks [51], by regulating their number, shape, and protein content in response to changing environmental conditions [52], have the intrinsic ability to mediate and modulate H_2O_2-driven biological processes [53].

Free radicals/other reactive oxygen and nitrogen species show a double role, causing oxidative damage/tissue dysfunction and serving as molecular signals activating beneficial stress responses [54], [55]. H_2O_2 emerged as a major redox metabolite operative in redox sensing, signaling, and regulation [56]. Its action mainly depends on the cellular context, its local concentration, and the kinetics of its production and elimination [57]. Interestingly, long-lasting blood pressure lowering effects of nitrite are NO-independent and are mediated by hydrogen peroxide, persulfides, and oxidation of protein kinase G1α redox signaling [58]. Although H_2O_2 is a strong oxidizing agent, it can accumulate in cells and tissues to relatively high concentrations due to it

slow reaction kinetics with most biomolecules. The removal of excess H_2O_2 by antioxidant enzymes is therefore central in minimizing cellular damage [59].

Beside the endogenous H_2O_2 produced by immune cells to kill pathogenic microbes, to inhibit other competing bacteria, lactic acid bacteria also produce H_2O_2, using different enzymes that include pyruvate oxidase, lactate oxidase, NADH oxidase, and NADH flavin-dependent reductases [60]. There are indications that H_2O_2-producing lactobacilli in the intestine play an important role in the repair of intestinal damage [61], whereas H_2O_2-producing lactobacilli in the vagina control the growth of pathogenic bacteria and prevent tumorigenesis [62]. Unfortunately, pathogenic *Streptococcus pneumonia* (through SpxB) and *Streptococcus pyogenes* (through LacD) are also known to produce H_2O_2, possibly through the lactate oxidation pathway [63]. While the host interactions in general are unclear, it was shown that H_2O_2 released by *Streptococcus pneumonia* inhibits host inflammasomes and is responsible for pathogen colonization [64]. Blockage of inflammasome activation by the oral commensal H_2O_2-producing bacterium *Streptococcus oralis* was also reported [64].

There are numerous reports indicating the role of hydrogen peroxide in viral inactivation and in virus-host interaction. For example,

- Herpes simplex virus 1-associated catalase may protect the virus from inactivation in an oxidizing environment outside a host cell [65];
- Uncontrolled concentrations of H_2O_2 promote translation by the internal ribosome entry site element of hepatitis C virus in tissue-cultured cells through adaptation of oxidative stress in the host cell by mediating La cytoplasmic shuttling [66];

  The addition of polyethylene glycol-conjugated catalase increased the specific enzyme activity, which, in turn, along with a respiratory syncytial virus (RSV) infection decreased H_2O_2 in the airways, and had an important defensive impact on RSV-induced disease/pathology. Therefore, it was concluded that the addition of catalase might represent a new pharmacological approach that should be studied in humans for the prevention and treatment of respiratory infections caused by RSV [67];
- H_2O_2-producing lactobacilli in the vagina may control genital HIV-1 shedding [68], the growth of several pathogenic bacteria, and may prevent tumorigenesis [62]. Along these ideas, Krüger and Bauer showed that the lactobacilli-origin H_2O_2 intrinsically is not likely to assist the vaginal epithelium, as it origins apoptosis both in non-transformed and in transformed cells [69]. The authors suggested that a combination of lactobacilli and peroxidase, that is, the situation actually found for tumor tissue *in vivo*, leads to the conversion of H_2O_2 to HOCl which does not affecting on non-malignant cells. When malignant cells, due to the abundance of extracellular peroxide anions, allow the formation of apoptosis. Subsequently, the combination of peroxide producing lactobacilli and peroxidase causes the selective elimination of malignant cells [69].

Discussion

Clinical trials and experimental studies have shown that probiotics, their components, or their sterilized variants (paraprobiotics) may be successfully used as biotherapeutic agents for the prevention and treatment of gastrointestinal diseases [70], [71], [72], [73], [74], and for resistance enhancement in case of intestinal viral infections [75], [76]. The possibility of mitigating antimicrobial resistance, which might be a result of a nosocomial, COVID-19-related infection [77], through probiotics has also been discussed in publication [78]. A study on the impact of the probiotic "Narine" (Vitamaks-E, Armenia) on the number of antibiotic resistant gut commensal *Escherichia coli* in familial Mediterranean fever patients, an autosomal recessive inflammatory disease [79], showed that the probiotic therapy resulted in a reduction of the relative abundance of operational taxonomic units in the genus *Escherichia* and the number of multi-resistant *E. coli* isolates [78].

Appropriate inflammasome activation and appropriate concentration of hydrogen peroxide realized by bacteria [64] are vital for the host to handle foreign pathogens and tissue damage, while aberrant inflammasome activation can cause uncontrolled tissue responses, leading to various diseases, including autoinflammatory disorders, cardiometabolic diseases, cancer, and neurodegenerative diseases [80]. In short, research data indicate the important role of hydrogen peroxide in host microbe interaction. Therefore, the assessment of blood H_2O_2, blood catalase activities, and detection of inflammasome activity present promising indicators in recommending probiotics in COVID-19 and accompanying diseases.

Conclusions

Thus, socioeconomic and biological strategies are needed to combat COVID-19 [81], [82], [83]. The production of hydrogen peroxide might be considered as one of promising indicators in probiotic-recommendation in COVID-19 and its accompanying

diseases. We hope that continuing investigations will raise awareness of potential COVID-19 probiotic recommendations, highlighting the latest scientific information about COVID-19/probiotics, and the importance of determining the specific “criteria” for the recommendation of probiotics’ use in this disease.

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