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Review

Probiotics in the times of COVID-19*

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The time of COVID-19 pandemic focused the attention of scientist to recognise the complex medical symptoms of the disease, modes of infection and possible therapies. The organisms' response towards SARS-CoV-2 infection depends on many individual factors and the course of disease is described as unprecedented and complex. Numerous symptoms from the respiratory system, abnormalities in the gastrointestinal tract, stroke, liver damage and coagulopathy, among others, are accompanied by negative side effects of the pandemic lifestyle, including immunity depletion, overall fitness impairment, skin condition worsening, psychological and psychiatric consequences. There is an urgent need to seek all possible routes for assuring favouring conditions to build and support the organisms' microbiological barriers and enhance immunity, which will also help during the ongoing vaccination action. Probiotic Lactic Acid Bacteria (LAB) and environmental *Bacillus* species are microorganisms typically found in food products or dietary supplements, but also applied on body surfaces or technological surfaces at home and in the industry. Since the contemporary definition of probiotics points to positive health effects, it is of highest importance to follow strict regulations and standards of product manufacturing, especially in the times of biohazard risks and rising public distrust of therapies.

Keywords: probiotics, COVID-19, SARS-CoV-2, probiotics for immunity, dysbiosis, vaccination, probiotics safety, *Bacillus* sp., *Lactobacillus* sp., health claims for probiotics

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IT IS STILL TIME FOR PROBIOTICS

The past year of 2020 can be regarded as the time of battle between the good and evil forces of the microbiological world, clearly showing that a pandemic touches each human in different ways on this Earth. Why did it happen, how long will it last, how does it spread, what protection should be used – only few questions concerning the nature of the micro world became our main focus, while longing for „normality" of these days, when we didn't realise the threat can eventually be so close.

Yearly browser score from PubMed (https://pubmed.ncbi.nlm.nih.gov) in 2020 for COVID-19 entry hit 89,893 results, which can give the sense of how much the scientific wold has been involved and completely permeated with the pandemic issues, in comparison to e.g. the „measles" entry which returns with slightly above a thousand hits. In this situation of virus-focused attention, probiotic issues seem not to be abandoned though, hence 4,410 entries in 2020 is a fair score and many research teams contributed to the increasing pool of interesting peer-reviewed papers. This interest peaked over 3.5 times during the last 10 years and hopefully will continue, while authors point out the possible advances and promising applications of probiotics in the difficult times of COVID-19 pandemic (Singh & Rao, 2021).

Therefore, focusing on probiotics, according to a well spread contemporary definition they are living microorganisms, which when introduced in an adequate number to the human or animal body via different routes of administration, will provide beneficial health effects (Havenaar & Huis In't Veld, 1992). "Pro" comes from Latin meaning „for", while "biotic" is presumably derived from Greek biōtikos, which stands for „life, lively", and thus seems to be the right name for a group of microorganisms that potentially can be one of the health and life guarding barriers of the human organism.

Most typically recognised probiotic species in the European countries are those found in the dairy food products, with bacteria originating from the *Lactobacillus* genus, with *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei,* as well as from the *Bifidobacterium* strains, such as *Bifidobacterium lactis* or *Bifidobacterium breve* (Joshi & Singh, 2012) being among the most common. Second meaningful group of bacterial probiotics is the *Bacillus* genus, with commonly mentioned *Bacillus subtilis*, *Bacillus coagulans*, *Bacillus pumilus*, *Bacillus licheiformis*, and *Bacillus clausii* (Jeżewska-Frąckowiak *et al.*, 2018). These species are still a rising field of scientific interest and constitute a broad potential for industrial applications, while commonly found in the Asian and West African *Bacillus* fermented foods (BFFs), based on soybeans and locust beans, just to mention miso, natto, chungkookjang, and dawadawa (Kimura & Yokoyama, 2019). Being environmental strains of outstanding growth condition tolerance, they are willingly adapted not only for direct consumption with food or as dietary supplements, but are also applied on body surfaces

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***This paper is dedicated to Professor Wacław Tadeusz Szybalski on the 100th anniversary of his birth**

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Abbreviations: ARDS, acute respiratory distress syndrome; BFFs, *Bacillus* fermented foods; CAPA, COVID-19 associated pulmonary aspergillosis; EFSA, European Food Safety Authority; FDA, Food and Drugs Administration; FSA, The Food Safety Asia; GC-MS, Gas chromatography-mass spectrometry; GIT, gastrointestinal tract; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LAB, Lactic Acid Bacteria; LPSs, lipopolysaccharides; MAIT, Mucosal-associated invariant T; MPro, main protease; RA, relative abundance; SCFAs, single chain fatty acids; 3CLpro, 3-chymotrypsin-like main protease or technological surfaces at home and in the industry. Their ability to form durable spores serves as an ideal model for prolonged storage as dried powder or in the microencapsulated form (Chávarri *et al.*, 2012; Yao *et al.*, 2020), as well as an intrinsic ingredient of chemical formulas: gels, soaps, pastes, sprays, liquids of various characteristic, emulsions, and concentrates (Jeżewska-Frąckowiak *et al.*, 2019, Stone *et al.*, 2020).

Regarding the mentioned probiotic species, the time of the health threatening SARS-CoV-2 pandemic is a particularly important moment to re-evaluate expectations from a scientific and industrial perspective, as well as fulfil social demands towards the features and quality of probiotic containing or derived products.

THE MATTER OF IMMUNITY – COMPLEX MEDICAL SYMPTOMS IN SARS-COV-2 INFECTION

Let us briefly describe the medical conditions connected with SARS-CoV-2 infection. The virus itself causes a pneumonia-associated respiratory disorder, known as COVID-19 (Chakraborty *et al.*, 2020). Not only the respiratory system suffers, since the mainly reported symptoms are fever (98.6%), dry cough (59.4%), fatigue, myalgia or headache, sometimes with abnormalities from the gastrointestinal (GIT) tract, including pain, vomits, diarrhoea, nausea. Moreover, several pathological syndromes from different body systems are observed, with stroke (Hess *et al.*, 2020), liver damage (Fan *et al.*, 2020) and coagulopathy (Marchandot *et al.*, 2020). The overall organisms' response towards SARS-CoV-2 depends on many individual factors, such as age, gender and coexisting diseases, while the disease course is described as unprecedented and complex. A complex combination of the humoral immune response, cellular immune responses (T-cell response, cytotoxic T cells and T helper 1 cells) and the so called 'core' COVID-19 immune signature: increased levels of cytokines IL1α, IL1β, IFNα, IL17A, is observed in patients (Brüssow, 2020). The immunological COVID-19 response may be extremely complex, surprisingly triggering even type III immunity with increased levels IL17, observed in autoimmune disorders, such as psoriasis, asthma or even cancer progression (Brüssow, 2020; Roncati *et al.*, 2020). Therefore, many hypotheses are concerned, with viral sepsis hypothesis (increased interleukin IL6 levels), cytokine storm hypothesis (cytokines TNFα and IL6, inflammatory cytokines), inflammation and thrombosis (proinflammatory markers, including the Creactive protein, MX1, IL6, IL1, IL8, TNFα, and NFϰB) among others (Brüssow, 2020; Amatya *et al.*, 2017).

PANDEMIC RELATED HEALTH ISSUES – DISTURBED MICROBIAL BALANCE

Regarding the fact that the COVID-19 disease can take a serious life-threatening form and it is still difficult or impossible to predict the severity of symptoms in specific individuals, the uncertain reality impacts almost all the fields of our personal, social, and work life, and we still have to face the fact that it will not be only a transient obstacle, related to the on-going infection, quarantining, and changing lifestyles during pandemic. In fact, we will face long term effects, which can be economical, social, educational, and significantly – psychological and medical. The latter ones result among others from limited or even temporarily blocked access to healthcare, whereas we will cope with the post COVID-19 symptoms, as well as with massive side effects of the pandemic lifestyle, including immunity depletion, skin condition worsening, overall fitness impairment, psychological and psychiatric consequences of triggering reality (Bashier *et al.*, 2021) or even a transient jam in the measles or polio disease eradication programmes (Durrheim *et al.*, 2021, Thompson & Kalkowska, 2021).

The disturbed microbiological balance – the dysbiosis state in case of ongoing COVID-19, involves, among others, lung disease related pulmonary aspergillosis (CAPA), whose cases are reported in hospitalised patients administered with the severe acute respiratory distress syndrome (ARDS), administered corticosteroids (Machado *et al.*, 2021) and treated with immunomodulatory drugs or Janus kinase inhibitors (Armstrong-James *et al.*, 2020). Moreover, numerous authors report that app. 72% to 100% of patients treated for COVID-19 are simultaneously cured with antimicrobial agents, such as azithromycin, hydroxychloroquine, moxifloxacin, cephalosporins, quinolones, macrolides, carbapenems, linezolid, cefoperazone-sulbactam, vancomycin with cefepime, levofloxacin, broad spectrum antibiotics and a caspofungin – agent (Armstrong-James *et al.*, 2020; Sultana *et al.*, 2020; Arshad *et al.*, 2020, Rawson *et al.*, 2020). The procedure is quite widespread, although there is a rather sparse published data describing the real state of bacterial/fungal COVID-19 coexisting infections, generally due to lack of diagnosis (Rawson *et al.*, 2020). If tested, predominant bacterial or fungal coinfections indicate *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aureginosa*, and *Candida* (Rawson *et al.*, 2020).

Merely touching on the complexity of health and wellbeing situation, it is worth to mention a few accompanying diseases and problems connected with the quarantined life style, where depression or anxiety are rising in the psychological or psychiatric field (Tang *et al.*, 2021). Depression is strongly intertwined with many physiological impairments, not to mention gastrointestinal disorders, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) (Holtmann *et al.*, 2016), allergies, type 1 diabetes, rheumatoid arthritis or psoriasis (Hidalgo-Cantabrana *et al.*, 2019; Winter *et al.*, 2018). The mentioned issues are the effects of dysregulated gut-brain-skin axis balance, strongly connected with the correlation between intestinal microbiota, systemic inflammation status and emotional states. A meaningful example is the overlapping mechanism of psoriasis-increased inflammatory cytokines IL-1, IL-6, IL-17, TNF-α, leading to increased indoleamine 2,3-dioxygenase levels, enhancing kynurenine bioformation and depression outcome (Wang *et.al.*, 2021). Inflammatory related gut barrier failure and disturbed balance in the number and diversity of intestinal microbiota, particularly the overrepresentation of *Bacteroidetes* phylum, eventually triggers the translocation of harmful bacteria and their toxins, including Gram-bacterial lipopolysaccharides (LPS), resulting in their release into the blood and body tissues. Therefore, depression episodes are reported to increase the C-reactive protein levels, as well as inflammatory TGF-β, IL-1β, TNF-α, IL-17, IL-21 cytokines.

Another pandemic health issue is massive worsening of the skin condition. In the COVID-19 times, the excessive use of alcohol-based cleaning products for hand rubs, along with frequent handwashing with soap and detergents (Patruno *et al.*, 2020) noticeably impair the skin barrier, causing dryness, irritation, itching, fissuring and bleeding. This in turn may lead to local erythema, both on the damaged atopic skin and the previously healthy one. It is found to be especially aggressive when the combination of water and alcohol exposure is applied (Alves *et al*., 2020). The mentioned conditions are typically most relevant in case of healthcare workers, among whom even 97% are reported to show lesions on hands, cheeks, forehead, and nose bridge, which are related to hygienic procedures and mask wearing. These damages are prior causes of infection – the skin microflora is greatly affected or even put in the dysbiosis state. The microbiome of a healthy skin, predominantly consisting of the *Actinobacteria*, *Firmicutes*, *Bacteroidetes*, and *Proteobacteria phyla*, is disturbed and prone to spreading pathogenic infections of *S. aureus*, *Helicobacter pylori*, or β-hemolytic *Staphylococcus epidermidis* (Bustamante *et al*., 2020).

PROBIOTICS AS ESSENTIAL MICROBIOTA – STIMULATING AND BARRIER FUNCTIONS

Under the above described difficult conditions, the role of commensal microbiota and probiotic microbiota is not to be overestimated. After listing only a few medical issues connected with SARS-CoV-2 infection, there is a range of possible fields for probiotic applications and potential health benefits.

The positive role for probiotic microbes is stimulating the immunity through the complex mechanism of pattern recognition receptor, sometimes called priming the mucosal immune system (Freitas & Silva, 2014; Maschirow *et al*., 2019) or triggering the „trained innate immunity" (Yakabe *et al*., 2021). This mechanism is directly connected with the presence of bacterial antigenic components, such as lipopolysaccharides (LPSs) or β-glucans. A similar pattern is utilised when it comes to vaccination. Probiotics seem to be promising immunomodulators in the COVID-19 infection, which has been shown towards viral infections on animal models in pre-clinical trials with LAB strains, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus fermentum* or *Lactobacillus brevis,* among others (Singh & Rao, 2021). Recent detailed findings show a direct link between the SARS-CoV-2 cellular entry process and the angiotensin-converting enzyme (ACE2) (Letko *et al*., 2020; Zhou *et al*., 2020). ACE2 mRNA is typically found to be massively expressed in the gastrointestinal system, particularly in the *ileum*, *jejunum* and *duodenum,* during intestinal inflammation, as well as in the lung (Harmer *et al*., 2002; Xiao *et al*., 2020, Yan *et al*., 2020).

Intestinal microbes enhance the levels of mucous membranes' T cell and IgA immunoglobulin A cells, along with serum immunoglobulin levels, thus regulating the commensals' presence inside the GIT, preventing bacterial translocation from the intestine and inflammation. Germ free animals show impairments and defective development of lymphoid structures, a reduced number and dimensions of lymph nodes and antibody production failure (Freitas & Silva, 2014; Maschirow *et.al*., 2019). Moreover, the haematopoiesis, also circulation of the immune cells and their activity in GIT-distant body sites are strongly intertwined with the presence of microbiota derived mediators, such as acetates, propionates, butyrates, and single chain fatty acids (SCFAs) (Maslowski *et al*., 2009; Maschirow *et al.,* 2019). SCFAs high levels, related to the abundance of *Bifidobacterium* or *Lactobacillus* sp. promote an increase in the IgG levels, while the secretion of IgA and IFN-γ was proven to be connected with *Bifidobacterium longum* BB536 levels (Yakabe *et al*., 2021). There is also a great impact of the microbiota on the lung antimicrobiological immunity, increasing the host's tolerance to specific infections, thus protecting from infection induced pathologies (Freitas & Silva, 2014; Maschirow *et al*., 2019).

Several authors have shown that the presence of TLR2-activating bacteria in the upper respiratory tract has the ability to regulate and attenuate lung injuries resulting from influenza. This mechanism is correlated with IFN-induced antiviral macrophage activation by the host microflora (Wang *et al*., 2013), while proper colonisation of certain intestinal *Escherichia coli* strains protects from an inflammation wasting syndrome co-existing with *Burkholderia thailandensis* lung infections. Tests involving fecal adoptive transfer model indicated that resistance against *K. pneumoniae* infections has increased, due to lowered anti-inflammatory cytokine IL-10 production in gut microbiota rich mice, while alcohol feeding strongly affects the intestinal dysbiosis, thus impairing the host defence against pulmonary *K. pneumoniae* infection provoked in germ free mice, recolonised with intestinal microorganisms derived from the alcohol (ethanol) fed individuals. Connections between alcohol-mediated dysbiosis and pulmonary host defence are determined by measuring chronic alcohol consumption effects on the organism's microbial status. The applied biochemical model of alcohol liquid diet consumption resulted in blood alcohol concentrations of 200 mg/dL, while binge- model alcohol consumption led to 400 mg/dL of alcohol in blood after 6 hours (Samuelson *et al*., 2017). Mucosal-associated invariant T cells (MAIT), a subclass of T lymphocytes, are determined to be highly present in the liver and are activated by the microbiologically synthesized riboflavin, while typically involved species are pathogens, *K. pneumoniae* or *S. aureus*, but also beneficial species or commensals, such as *Lactococcus lactis*, *Saccharomyces cerevisiae* or *E. coli* (Gebru *et al*., 2021). Clinical trial examples of direct connection between probiotic supplementation and a good recovery prognosis cover mechanically ventilated patients, administered with *L. rhamnosus* and *B. subtilis*, resulting with less frequent case of ventilator-associated pneumonia (Larenas-Linnemann *et al*., 2020).

In the context of SARS-CoV-2 infections, even more striking findings are presented in the literature, involving high-throughput sequencing of the V3-V4 hypervariable region of the 16S rRNA gene, serving for identification of bacterial and archaeal strains and estimation of the microbiome diversity (Bukin *et al.,* 2019; Gu *et al*., 2020). It has been determined that a set of data regarding the abundance and composition of gut microbiota status can be a potential biomarker for recognising the complete disease characteristics of COVID-19 and even to distinguish it from other coronavirus infections, such as influenza A (H1N1). This was assayed by assessing a group of laboratory confirmed real-time reverse-transcription PCR diagnosed patients with clinical symptoms that were neither antibiotic, probiotic, nor both treated for a month before testing. Dysbiosis and reduced diversity of gastrointestinal tract has been determined in COVID-19 patients, revealing a higher relative abundance (RA) of bacteria from the *Streptococcus*, *Rothia*, *Veillonella*, *Erysipelatoclostridium* and *Actinomyces* genera of opportunistic pathogens (Gu *et al*., 2020; Luo *et al*., 2021), while a significantly decreased diversity and relative abundance of beneficial species, such as *Bifidobacterium* or *Lactobacillus*, was noted (Luo *et al*., 2021). This characteristic microbiota state has been monitored and found to be persistent, with depleted symbionts and gut dysbiosis even after clearance of SARS-CoV-2. On the other hand, interesting findings reported by Luo and coworkers (Luo *et al.*, 2021) suggest that the appropriate use of pre- and probiotics, along with early life exposure to soil-rich environment, including a variety of *Proteobacteria* species, can together be crucial factors for reducing a severe response to viral infections, as it is observed in bats, naturally occurring reservoirs of coronaviruses.

During the on-going vaccination action (Petousis-Harris, 2020; Kuehn, 2021), there is a promising strategy for designing the future vaccination outlines and schedules, involving probiotic species and the way they train the „innate immunity" (Yakabe *et al.*, 2021). Efficient vaccine specific proliferation of T-cell lines, connected with oral or injection vaccines, is strongly intertwined with the abundance of species from the *Actinobacteria* phylum, including *Bifidobacterium* sp.

Although it is quite too early yet to assess long-time effects and values of the probiotic species strategies towards SARS-CoV2 infection, this subject is scientifically sound and in terms of vaccination concerns native strain supplementation, as well as a recombinant probiotics vaccine development (Al-Ansari *et al.*, 2021; Moradi-Kalbolandi *et al.*, 2021). Biotechnological strategies are developed to utilise environmental *Bacillus* species, including *B. subtilis,* but also those not assigned as probiotics yet. Among the latter ones, *Brevibacillus formosus* extract prepared from soil samples was GC-MS screened and computationally analysed *via* molecular docking in search for bioactive compounds, including proteases or their inhibitors involved in the virus life cycle, e.g. inhibitors against 3-chymotrypsin-like main protease (3CLpro) or main protease (MPro) (Alam *et al.*, 2021). Moreover, thermophilic *Bacillus stearothermophilus* (currently reclassified as *Geobacillus stearothermophilus*) is a research model for the development of novel bionanotechnologies, involving modified TP-84 bacteriophage. Phage display of concatemeric proteins has a potential in vaccine construction and other programmable scientific, biomedical and industrial functions, including regeneration or drug delivery (Skowron *et al.*, 2018; Skowron *et al.*, 2020; Łubkowska *et al.*, 2021). Still, much research must yet to be done.

Finally, in order to present the range of possible health benefits resulting from probiotics' potential in pandemic outbreaks, it is worth to mention the value of beneficial microflora for epidermis condition (Roudsari *et al.*, 2015), antioxidant skin protection utilising lactosporin (Majeed *et al.*, 2020) or enhancing skin permeability for topical treatment with an alkaline protease (Nounou *et al.*, 2017). Thus, the skin treatment products can be enriched with probiotic cells, possibly with addition of prebiotic substances, or contain probiotic derived bacterial enzymes, bacterial metabolites, or even consist of biotechnological products derived from probiotic cells. The protective skin barrier can be restored with methods involving bacteriotherapy, with potential of healing various damages, covering eczema, atopic dermatitis, acne, allergic inflammation, hypersensitivity, UV-induced damage, and wound protection (Roudsari *et al.*, 2015). The proposed species involve *B. subtilis*, along with *B. subtilis* alkaline protease, *B. coagulans* derived Lactosporin or *Lactobacillus* sp. (*L. acidophilus*, *L. casei*, *L. plantarum*, *L. gasseri*) with an addition of inulin or konjac glucomannan hydrolysate. *L. paracasei* is proven to reduce skin inflammatory processes (Bustamante *et al.*, 2020; Wieërs *et al.*, 2020), while *Bacillus amyloliquefaciens* SCGB1 fermented soybean (cheonggukjang) has been shown to reduce atopic dermatitis in mouse models (Cho *et al.*, 2019).

DEMANDS AND EXPECTATIONS – QUESTIONS OF RESPONSIBILITY

During the COVID-19 pandemic there is much chance that spreading the knowledge and consciousness about probiotics can help to improve general health status and build individuals' immunity, but there is also a great challenge in sustaining the highest microbiological quality of probiotic products. This particularly refers to those from the *Bacillus* genus, of which several pathogenic species are known, including *Bacillus anthracis*, *Bacillus cereus* and *Bacillus weihenstephanesis* (Bradley & Sauberan, 2008; Jezewska-Frackowiak *et al.,* 2018). Since the contemporary definition of probiotics points to the positive health effects, it is of highest importance to follow strict regulations and standards of product manufacturing, which is intrinsically connected with trustworthy labelling and responsible distribution (Regulation (EC) No. 1924/2006; EFSA meeting with IPA Europe, 2019).

Unfortunately, still, many probiotic products are bearing serious defects, tend to be poorly described, include misleading strain names or names of even non-existing species, or the declared species cannot be detected with gold standard methods of 16S rRNA sequencing, raising doubts as to the reliability of a given manufacturer and the probiotic itself.

Legislative and controlling bodies, such as the European Commission along with its scientific expertise body of independent experts – EFSA (European Food Safety Authority), as well as the US Food and Drugs Administration (FDA) or The Food Safety Asia (FSA), associating product safety institutions in Asia, Pacific and the Middle East, should all take in count the increasing interest in probiotic products and the spreading range of their applications. The crucial demand is to assure the quality of probiotic preparations and provide full information of the actual microbiological status, as well as informative campaign to raise full awareness of the source and actual mode of action. Almost unlimited access to numerous sources of information is not always paired with the ability to judge their value (Scherer *et al.*, 2021), therefore it is also the great responsibility of the manufacturer to provide a product with declared and comprehensive health claims (EFSA meeting with IPA Europe, 2019). It is of a particularly high importance in the present situation of biohazard risks and rising public distrust of scientific and legal status of microorganisms, therapies, vaccines, food neophobia, and unfamiliar products' trigger (Faccio & Fovino, 2019; Aarøe *et al.*, 2016; Patterson, 2009; Elleray, 2021; Asaaga *et al.*, 2021). Moreover, authorisation rights, such as copyrights, patent status, confidential information, and intellectual property are understandable reasons that the suppliers keep trade secrets, however it cannot interfere with the consumers' right to full information and microbiological status of the product.

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