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Immunomodulatory meaning of diet and COVID-19

Immunomodulacyjne znaczenie diety i COVID-19

Dominika Grońska[1,A-D,F], **Monika Kłujsza**[1,B,D,F], **Aleksandra Pelczar**[1,B,D,F], **Jolanta Kaszuba-Zwoińska**[1,E-F]

[1] *Department of Pathophysiology, Collegium Medicum, Jagiellonian University, Kraków, Poland*
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Abstract

Introduction and Objective. The latest scientific reports showed that there is a relationship between the state of the gastrointestinal tract and the immune system, and the incidence of COVID-19. Diet can exert an immunomodulatory effect and regulate the immune response of an organism. The aim of the review is to show the effects of immunomodulators contained/supplemented in a diet on the infection SARS-CoV-2 and the course of COVID-19.
Review Methods. The literature review was conducted using PubMed, Google Scholar and the Medline database.
Results. Regular vitamin D supplementation significantly reduces the risk of respiratory infection with SARS-CoV-2; vitamin C may inhibit the expression of the ACE2 receptor in human small alveolar epithelial cells and limit the penetration of SARS-CoV-2; reduced iron levels predispose people to severe COVID-19 symptoms; selenium deficiency may be responsible for a decreased level of antibodies and NK cell cytotoxicity. Aloë vera isolated polysaccharides strengthens the immune system; the quercetin and ellagic acid in combination with virus proteins show potential antiviral activity against SARS-CoV-2. Subsequently, adaptogens, ginger, echinacea and curcumin - showed anti-inflammatory effects. Also, the optimal composition of the gut microbiota improved/maintained the integrity of the lymphoid tissue found in the gastrointestinal tract (GALT) and the functioning of the gut-pulmonary axis.
Summary. Natural immunomodulators may be a relatively safe therapeutic option in patients during the course of COVID-19, but there are still no official recommendations for their practical use in therapy. It should be emphasized that there is a need for further scientific research into the mechanisms of action and efficacy of phytotherapy in the context of the effectiveness of plant-based immunostimulants in alleviating the course of COVID-19 disease.

Key words

vitamins, probiotics, diet, microelements, COVID-19, plant immunostimulants

Streszczenie

Wprowadzenie i cel pracy. Najnowsze doniesienia naukowe wykazały, że istnieje związek pomiędzy stanem układu pokarmowego i odpornościowego a występowaniem COVID-19. Dieta może wywierać efekt immunomodulacyjny i regulować odpowiedź immunologiczną organizmu. Celem niniejszego przeglądu jest przedstawienie wpływu immunomodulatorów zawartych w diecie bądź suplementowanych na zakażenie SARS-CoV-2 i przebieg COVID-19.
Metody przeglądu. Przegląd piśmiennictwa przeprowadzono z wykorzystaniem wyszukiwarek PubMed i Google Scholar oraz bazy danych Medline.
Opis stanu wiedzy. Regularna suplementacja witaminą D znacząco zmniejszała ryzyko zakażenia układu oddechowego wirusem SARS-CoV-2; witamina C może hamować ekspresję receptora ACE2 w ludzkich komórkach nabłonka małych pęcherzyków płucnych i ograniczać penetrację SARS-CoV-2; obniżony poziom żelaza predysponuje do wystąpienia ciężkich objawów COVID-19, niedobór selenu może odpowiadać za obniżony poziom przeciwciał i cytotoksyczność komórek NK. Wyizolowane polisacharydy z Aloe vera wzmocniły układ odpornościowy; kwercetyna i kwas elagowy w połączeniu z białkami wirusa wykazały potencjalną aktywność przeciwwirusową wobec SARS-CoV-2. Kolejno substancje adaptogenne, imbir, echinacea oraz kurkumina – wykazywały działanie przeciwzapalne. Również optymalny skład mikrobioty jelitowej poprawiał/utrzymywał integralność tkanki limfatycznej występującej w obrębie przewodu pokarmowego (GALT) i funkcjonowanie osi jelitowo-płucnej.
Podsumowanie. Naturalne immunomodulatory mogą stanowić stosunkowo bezpieczną opcję terapeutyczną u pacjentów chorujących na COVID-19, jednak nadal nie ma oficjalnych zaleceń dotyczących ich praktycznego wykorzystania w terapii. Należy podkreślić, że istnieje potrzeba prowadzenia dalszych badań naukowych nad mechanizmami działania i skutecznością fitoterapii w kontekście skuteczności roślinnych immunostymulatorów w łagodzeniu przebiegu choroby COVID-19.

Słowa kluczowa

witaminy, dieta, probiotyki, mikroelementy, COVID-19, immunomodulatory roślinne

✉ Address for correspondence: Dominika Grońska, Department of Pathophysiology, Collegium Medicum, Jagiellonian University, Kraków, Poland
Email: dominika.gronska.dietetyk@gmail.com

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INTRODUCTION AND OBJECTIVE

Since December 2019, the SARS-CoV-2-triggered pandemic has challenged the world of sciences, medicine, immunology, and related fields to determine a new perspective, emphasizing the importance of maintaining the good health status of an organism to prevent various types of disorders and diseases related to the immune system. Before the SARS-CoV-2 pandemic, mild or acute respiratory infections were caused by the zoonotic coronaviruses – SARS-CoV-2 in 2002 and MERS-CoV in 2012. Both SARS-CoV-2 use the ACE-2 receptor to enter the cell [1, 2], and Fcγ receptors on macrophages. ACE-2 receptors are expressed in the kidneys and the gastrointestinal tract, organs that contain remnants of SARS-CoV-2 [2]. Clinical studies showed that SARS-CoV-2 coronavirus RNA was detectable in respiratory secretions and stools of some patients up to even one month after the onset of the disease [3]. Recent reports indicate that there is a clear link between the digestive system, the immune system, and the development/course of COVID-19 [4–6]. The results of scientific studies confirm that a properly balanced diet, its composition, sources of nutrients, macro- and microelements, play a key role in the functioning of the immune system [1, 3]. Diet, through various effects exerted on metabolic processes at the cellular and subcellular level, can exert an immunomodulatory effect, regulate the immune responses and the metabolic processes involved in fighting pathogens, and regenerate tissues after damage caused by infection. The immunomodulatory effects of diet can be observed in the form of the integrity of the body's physical barriers (e.g. intestinal mucosa), the constitution of the microbiome, and the functioning of the immune system (e.g. activation of macrophages, T and B lymphocytes). In dietetics, there is a concept of immunomodulating substances – immunomodulators, which encompass various bioactive substances that activate immune response engaged cells and/or mechanisms of innate and acquired immunity.

Th aim of the review is to show the effects of immunomodulators contained/supplemented in a diet on the infection SARS-CoV-2 and the course of COVID-19.

REVIEW METHODS

This paper is based on a review of the Polish and foreign-language literature available in PubMed, Medline and Google Scholar from 2019–2022. Only full, original and review papers were included in the review.

STATE OF KNOWLEDGE

Immunomodulating vitamins and microelements. SARS-CoV-2 infection and COVID-19 disease affect the immune system, innate and acquired mechanisms. A balanced diet is crucial for the proper functioning of the immune system and the maintenance of body health. It is known that nutritional deficiencies affect the immune system during an infection [7]. Vitamins and selected micronutrients that are supplied or supplemented with food have a positive effect on reducing viral load and hospitalization of patients with COVID-19 [7]. In the group of vitamins that have a special effect, the vitamins D, A, E, C microelements must be distinguished. Vitamin D3 has been the subject of greatest interest in scientific research for many years – as it acts pleiotropically on metabolic and signaling pathways in the body, and strengthens the body's defensive responses, which is particularly important in the era of the COVID-19 pandemic. Vitamins A, D, E, C should be part of the diet of every human being due to their effect on the immune system [8].

Vitamin D. The best source is exposure of the skin to sunlight, where it is synthesized and extracted from food. Vitamin D3 deficiency is widespread, not only in Germany, but also all over the world. Vitamin D3 has been in demand for many years, but the particular benefit of an adequate supply is attributed to the COVID-19 pandemic. Persons over 65 years of age, in whom the blood level of 25 (OH) 2D3 decreases, are highly affected [8]. Vitamin D3 enhances the effect of monocytes and macrophages in the fight against pathogens, which are an important component of the body's own defense reactions – the course of a normal immune response [9, 10]. Research results show that supplementation with vitamin D3 significantly reduces the risk of respiratory tract infections, demonstrating the protective effect of vitamin D3. In addition, clinical studies have shown that the condition of SARS-CoV-2-infected patients with vitamin D3 deficiency deteriorated significantly [11, 12].

Vitamin C. The role of vitamin C in supporting the immune system was first discovered in the 1930s when seafarers suffered from a disease called scurvy [Scurvy has been well known and documented since the 13th century] [7]. Vitamin C has usually been associated with treating a cold during the autumn and winter when immunity decreases. Positive effects include antioxidant, immunomodulatory, antiviral and anticoagulant effects [8, 13]. The effect of vitamin C in COVID-19 is associated with oxidative stress and/or severe inflammation [14, 15]. Vitamin C deficiency weakens immunity and leads to an increased susceptibility to infection, which further aggravates the disease and increases the risk of pneumonia [15, 16, 17]. In combination with other natural compounds (baicalin and theaflavin), vitamin C may inhibit the expression of the enzyme ACE2 in the small cells of the human lung epithelium and restrict the penetration of SARS-CoV-2 into the cell [17, 18].

Vitamin E. Vitamin E is known as the strongest antioxidant, which is why it is called the 'vitamin of youth' for good reason. In addition to antioxidant and anti-inflammatory functions, it also has an immune function [8, 19]. Increased vitamin E supplementation supports the immune function of the lymphocytes, optimizes the Th1 population, and suppresses the Th2 type reaction. Vitamin E supplements may reduce the production of superoxides and positively influence the treatment progress of COVID-19 patients. It has also been shown that supplementation with this vitamin increases immunity against respiratory infections [10, 19].

Vitamin A. Particularly known as retinic acid, it acts as an effector of T cells and supports adaptive and innate immunity. Vitamin A is attributed to play a special role in the process of vision and in strengthening the action of the immune system [20]. Because COVID-19 disease leads to inflammation called hyperinflammation which causes the vitamin A stores run out, supplementation is required during convalescence. In addition, vitamin A deficiency has been found to limit the ability of the lungs to restore damaged epithelial surfaces, leading to pulmonary fibrosis and reduced capacity [20, 21].

Zinc. Zinc is an element that is usually associated with affecting hair, skin and nails. Its effects – as it turns out, are much wider, as it also affects the immune system. It has immunomodulatory and antiviral properties used in the supportive treatment of patients with COVID-19. Its deficiency is associated with a dysfunction of the immune system and an increased susceptibility to infectious diseases. Zinc plays a crucial role for both the innate and the acquired immune system. In addition, it has antioxidant properties that protect the body from reactive oxygen species. Therefore, the correct concentration of zinc in the body offers a possible mechanism for its action as an anti-inflammatory compound, which optimizes the immune response and further reduces the infection rate [8, 22]. Recent studies of zinc-dependent viral enzymes required to initiate an infectious process have shown that zinc levels are directly related to a mild course of COVID-19. The results of four hospitalized patients diagnosed with COVID-19 showed that their symptoms were alleviated after treatment with high oral zinc salts (15–23 mg/d), suggesting that treatment with high doses of zinc may be a therapeutic option for SARS-CoV-2 patients [23, 24].

Iron. Iron is an element that is usually associated with iron deficiency anaemia. In addition, it is used to support the function of the immune system. Iron is involved in several immune processes and is also an essential component of enzymes involved in the activation of immune cells. The atomic structure of iron makes it a mediator of oxidative stress, and is responsible for the synthesis of highly toxic hydroxyl radicals against infectious agents. Decreased iron levels are associated with reduced efficacy of immune cells (NC cells and lymphocytes) and reduced production of cytokines. Low iron levels in patients with COVID-19 have been shown to predispose them to severe symptoms from a SARS-CoV-2 infection. However, by monitoring iron levels, the severity of the disease and even mortality can be predicted [23]

Selenium. Selenium is an element necessary for the proper functioning of the immune system. It participates in the mechanisms of the acquired immune response, supporting the production of antibodies [8]. Hence, the deficiency may lower the level of antibodies in the body, weaken the cytotoxicity of NK cells, and thus the cellular immunity and the response to vaccination [18]. Selenium supplementation may enhance the immune response to SARS-CoV-2 infection. Additionally, latest studies have shown that vitamin D3 and selenium deficiency are found in patients with acute respiratory infections [21].

Plant immunostimulants. Plant preparations showing immunostimulating properties have been known for many years. They are referred to as Biological Response Modifiers (BMR) which are used to support the prevention and treatment of chronic infectious and inflammatory diseases. Currently, it is difficult to determine the exact number of plant immunostimulants [24, 25].

The complexity of the pathomechanism (hyperinflammation, hypercytokinaemia, forming immunocomplexes, NETy and enhancement of the antibody-dependent response – ADE) and clinical symptoms of COVID-19 disease suggests the need for pleiotropic therapy with the use of antiviral agents, immunostimulants, and even immunosuppressants or anticoagulants [26]. According to reports by Boozari and Hosseinzadeh [27], herbal drugs and supplements are recommended in prophylaxis, therapy [28], and after exposure to SARS-CoV-2. Therefore, this study reviews the most popular plant immunostimulatory substances with potential use as a support for therapy in patients in the course of COVID-19.

Aloë. Aloë belongs to the *Liliaceae* family. The most valued species are still *Aloë arborescens* (woody aloe), *Aloë vera* (common aloe), and also *Aloë xerox* (spiny aloe) [27]. Interestingly, the medicinal properties of aloe were appreciated by the ancient Egyptians and Sumerians [29]. Currently, its analgesic, anti-inflammatory, antibacterial and immunomodulatory effects are emphasized [30]. Moreover, as reported by Grace et al., aloe vera contains biologically-active compounds, which include vitamins B and C, folic acid, and a number of minerals [31]. Additionally, the plant is characterized by a high concentration of polysaccharides, the main one being acemannan with its strong immunomodulatory properties [32, 33]. Acemannan is a component of most of the mucous substances contained in *Aloë vera*, while the polysaccharides isolated from *Aloë vera* support the immune system by influencing the secretion of IL-1, IL-6, TNF-α and INF-γ. The aforementioned compounds stimulate the growth of fibroblasts and increase the ability of macrophages to phagocytosis [32, 33]. The very mechanism of action is based on the activation of mannose receptors, and consequently the activation of macrophage NO synthase [30]. Importantly, acemannan can significantly induce the maturation of immature dendritic cells [34]. Another breakthrough study was Białas-Chromiec et al., where P-2 lectin was isolated from *Aloë arborescens*, which has the ability to stimulate the immune response [35]. According to the researchers, P-2 lectin has the ability to react with α2-macroglobulin, thanks to which it activates the component and proactivator of the C3 complement protein, which in turn stimulates B lymphocytes to produce antibodies [36, 37]. Hence, it is suggested to use aloe vera in prophylaxis, therapy and in the period after COVID-19, which may have an immunomodulatory effect.

Black chokeberry. *Aronia melanocarpa* belongs to the *Rosaceae* family and comes from the eastern parts of North America [38]. It was valued by Native Americans for making tea infusions for colds, and the bark was used as an astringent [39]. It is worth mentioning that the raw materials obtained from *Aronia melanocarpa* contain a large amount of various bioactive ingredients, including vitamins A, B, C, PP, E and minerals (Cu, Mn, Ca, Fe), as well as polyphenols, tannins and organic acids [40, 41]. However, the key factor is the anti-inflammatory, antitumour, antimicrobial and antiviral effects of products obtained from *Aronia melanocarpia* [42]. The already-mentioned anti-inflammatory effect consists in blocking the expression of induced nitric oxide synthase – iNOS and cyclooxygenase – COX-2, which in turn inhibits the release of PGE2 and the chemotactic protein for MCP-1 monocytes [43, 44]. Additionally, chokeberry reduces the expression of the ICAM-1 adhesion molecule on the endothelium and is responsible for the adhesion of monocytes to the endothelial surface in the inflammatory process [45]. On the other hand, anthocyanin pigments have the ability to reduce mast cell degranulation, thus regulating the flow in the capillaries, and these potentially have a beneficial effect on reducing local inflammation [46]. Jang et al. [47] provide interesting information on the use of the bioactive fraction of *Aronia melanocarpia* in the prevention and treatment of inflammatory diseases of the respiratory tract. The study by Chojanacka et al. [48] also showed that *Aronia melanocarpia* products are effective *in vitro* and *in vivo* against various subtypes of influenza viruses. Moreover, the quercetin and ellagic acid contained in the plant, in combination with viral proteins, showed potential antiviral activity against SARS-CoV-2, which may be useful in the treatment of COVID -19 patients [49].

Adaptogens. Adaptogens are pharmacologically active compounds or plant extracts derived from various plant species. They have the ability to increase the body's metabolic stability against physical stress without increasing oxygen consumption. They show a holistic effect. They affect the immune system and improve mental performance [50]. Plant adaptogens have been used by humans since ancient times, although the term 'adaptogen' itself was not introduced until 1947 [51]. In preclinical studies, anti-inflammatory, antiviral and antioxidant effects of selected adaptogenic plants have been demonstrated [52]. In addition, it is worth mentioning non-specific antiviral actions by influencing the mechanisms of innate cellular and humoral immunity, such as activation of defensins, the complement system, increasing the expression of pathogen-recognizing receptors, especially TLR (*Toll-like Receptors*) and interferon synthesis. It also decreased the expression of the pro-inflammatory cytokines IL-1, IL-2, IL-6, IL-8, TNF-α and activation of NK cells and phagocytic mucosal cells [48, 49, 50]. Moreover, products obtained from plants such as *Andrographis paniculata* (AP), *Eleutherococcus senticosus* (ES), *Panax* spp. (Ginseng, Psp), *Rhodiola rosea* (RR), *Schisandra chinensis* (SC) and *Withania somnifera* (Ashwagandha, WS) have the ability to act in many directions on the nervous, endocrine and immune systems, as well as their mutual regulatory interactions [53, 54].

Black elderberry. Black elderberry (*Sambucus nigra L.*) has long been used as a diaphoretic in the treatment of colds and as an antipyretic agent [55]. It includes, *inter alia,* anthocyanins, flavonoids (campferol, rutoside, quercetin, isoquercetin) and citric, malic and tartaric acids [56]. Elderberry has antiviral and immunomodulating properties [57]. *In vitro* studies show that elderberry products increase the production of the cytokines IL-1β, IL-6, IL-8 and TNF-α by monocytes activated with bacterial lipopolysaccharide [58]. Interestingly, the anthocyanins contained in *Sambucus nigra L.* potentially inhibit inflammation in a mechanism similar to the anthocyanins present in *Aronia melanocarpa* [59]. According to Mousa [60], in patients infected with influenza A and B virus who were administered 15 ml of elderberry extract 4 times a day, the infection lasted 4 days less than in the group receiving placebo. Unfortunately, despite the promising results obtained in randomized clinical trials on the treatment of viral infections, administration of elderberry preparations to patients in the course of COVID-19 is not recommended, as there is still no scientific data in this regard [61].

Common garlic. Common garlic (*Allium sativum L.*) has been widely used in medicine for thousands of years. The beneficial effects of common garlic include: antifungal, antibacterial, anti-inflammatory, antitumor, and most importantly – immunomodulating [62]. Garlic contains bioactive substances, such as allicin, S-allocysteine, diallyl sulfide and diallyl disulfide [63, 64]. According to Arreola et al. [64], the immunomodulatory properties of garlic result from the stimulation of NK cell activity, macrophage phagocytosis and activation of lymphocyte responses to cytokines and myogens. Additionally, sulfur compounds contained in *Allium sativum L.* have the ability to reduce the expression of NO synthase by macrophages [64]. A significant anti-inflammatory effect is also emphasized, resulting from the beneficial effect on the release of ICAM-1 intercellular adhesive particles and vascular VCAM-1, which are responsible for the adhesion of leukocytes to endothelial cells [65]. The most important bioactive compound found in common garlic is the aforementioned allicin, which has the potential to penetrate the cell interior and affect cytoplasmic components and enzymes. Moreover, it has the ability to block lipid and RNA synthesis in bacteria [64]. Interesting data is also provided by Choo et al. [66], who conclude that combination therapy: allicin and antimicrobial drugs, may be a real alternative to the problem of drug resistance in the course of infectious diseases in patients.

Ginger. The effect of medicinal ginger (*Zingiber officinale*) has been recognized since ancient times. Current scientific research provides a lot of evidence for the health-promoting effect of medicinal ginger used as a herbal medicine in the treatment of sore throat, indigestion, vomiting, fever and infectious diseases, which is closely correlated with its anti-inflammatory, anti-cancer, immunomodulating and anti-apoptotic effects [66]. The presence of gingerol, with its strong anti-inflammatory properties, in *Zingiber officinale* is of key importance [66, 67]. According to research, medicinal ginger has the ability to inhibit the activity of cyclooxygenases responsible for the synthesis of prostaglandins with the participation of gingerols, similar to the action of non-steroidal anti-inflammatory drugs. Ginger also has the potential to modulate pathways activated in chronic inflammation by inhibiting the action of genes involved in the inflammatory response and selected genes encoding the COX-2 enzyme, chemokines and cytokines [67]. Additionally, it may inhibit the synthesis of IL-2 by T lymphocytes and the expression of the gene encoding IL-2, and also increase the sensitivity of NK lymphocytes to the action of IL-2 [66, 68]. Studies conducted by Fouda and Berike [69] showed that ginger extracts administered to rats at a dose of 200 mg / kg / day reduced the level of pro-inflammatory cytokines IL-1β, IL-2, IL-6 and TNF-α. Hence, it has been suggested that products derived from medicinal ginger may have a potentially beneficial effect in the treatment of chronic inflammations [68].

Echinacea purple. *Echinacea purpurea* belongs to the *Asteraceae* family. Its healing properties were already used by Native American tribes in North America for, among others, treatment of respiratory diseases, and also used in the course of fever, infectious diseases, infections, and as an anti-inflammatory agent [70]. It is worth emphasizing that numerous studies clearly show the immunomodulatory effect of preparations obtained from echinacea. They increase the production of antibodies, support the phagocytosis process and activate lymphocytes through the increased secretion of cytokines. The mechanisms of immunostimulatory effects are not fully understood; presumably they are caused by the activity of polyphenols, polysaccharides, glycoproteins and alkamides contained in leaves, flowers and roots of *Echinacea* [70, 71]. It has been shown that supplementation with echinacea preparations reduces the production of TNF-α, while the secretion of IFN-γ and the macrophage chemotactic protein MCP-1 increases. Additionally, *Echinacea* preparations potentially increase the production of immunoglobulins and regulate the production of antibodies by increasing the secretion of cytokines by Th1 and Th2 helper lymphocytes. Chemical compounds contained in echinacea can stimulate the metabolic activity of granulocytes, thus increasing the number of CD16 + and CD56 + NK cells, and also affect the CD4 / CD8 lymphocyte ratio [61, 72]. Interesting data are provided by statistical studies conducted by meta-analysis by Schoop et al. [73], which assessed the effect of echinacea in the prevention of rhinovirus-induced colds. The results of the research showed that echinacea preparations do have a preventive effect in colds caused by rhinoviruses. On the other hand, Shah et al. [74] reported a beneficial effect of echinacea preparations in the prevention (reduction of incidence by 58%) and treatment of colds (reduction of infection time by 1–4 days). The effects of *Echinacea* preparations are confirmed by meta-analyzes from 2015, according to which supplementation with echinacea preparations led to a lower frequency of recurrent viral infections [75].

Turmeric. Turmeric (*Curcuma longa L.*) belongs to the ginger family and is grown mainly in Bengal, China, Taiwan and India. It is worth emphasizing that raw materials obtained from *Curcuma longa L.* show anti-inflammatory, antioxidant, immunostimulatory, antimicrobial and anticancer properties [76, 77]. One of the biologically-active substances found in the rhizome is curcumin, which has a significant therapeutic potential [76]. According to Pagano et al. [77], dietary supplements containing curcumin may exert systemic antioxidant effects, which may indirectly alleviate inflammation. Moreover, curcumin has been shown in research studies to be active against a wide range of viruses by disrupting the pathways that control cell penetration and signaling [78]. Zahedipour et al. [77] proved that curcumin potentially affects some pathophysiological features in the course of COVID-19, including viral penetration, cytokine storm associated pulmonary fibrosis and vascular coagulopathy. It has been proven that curcumin obtained from turmeric inhibits ACE2 receptors, thus inhibiting the entry of SARS-CoV-2 into the host cell [79]. Curcumin also has the ability to block release of the pro-inflammatory cytokines IL-1, IL-6 and TNF-α [80, 81]. Thus, supplementation with preparations derived from *Curcuma longa L.* seems to be a safe and effective form of supporting the therapy of patients in the course of COVID-19 [61].

In conclusion, there are no guidelines for the routine use of these substances in the prophylaxis and treatment of patients in the course of COVID-19. However, they can potentially be used in prophylaxis and as support in treatment. At the same time, the need is indicated for further, well-planned research on the mechanisms of action and effectiveness of phytotherapeutic interventions in the context of COVID-19.

Pre- and probiotics as immunostimulants. The skin, the urogenital system and the digestive system are the natural habitat for many billions of microbes in the body. Depending on the anatomical part and function, the area is populated by bacteria, fungi or viruses (e. g. phages), as well as by others. The best known and at the same time the most advanced ecosystem in terms of diversity and population is the microbiota of the gastrointestinal tract, in particular the oral cavity and the large intestine [1, 82]. According to the latest findings, it is known that the composition of the digestive tracts microbiota, especially of the colon, depends on many factors, including the type of nutrition, type of childbirth, therapies applied, and the stress [83, 84].

The GALT system (Gut-associated lymphoid tissue) – known as the intestinal immune system, is a lymphoid tissue of the mucous membranes in the gastrointestinal tract. Enterocytes form the majority of the cells of the intestinal epithelium and are able to absorb nutrients. Some enterocytes express Toll-Like Receptors and excrete a number of inflammatory chemokines (IL-8), cytokines (IL-1, IL-6, IL-7, IL-11 and TNF), as well as growth factors such as SCF and G-CSF (Granulocyte Colony Stimulating Factor). These molecules trigger the activation of peripheral neutrophils and mast cells and their migration into the subepithelial regions of the intestine; they also speed up the activation and differentiation of local lymphocytes. When a pathogen enters the body, the Panetha cells release antibacterial compounds which are crucial for maintaining the body's homeostasis into the intestinal lumen [85, 86].

These complex immunological processes in the GALT and gastrointestinal tract are also closely related to light-covering microbiota, microbiota metabolites and prebiotics that influence the development and growth of comensals. In the intestine, the genera *Bacteroidetes* and *Firmicutes* dominate, while the bacteria of the genera *Bacteroidetes*, *Firmicutes* and *Proteobacteria* dominate the lungs [6]. Experimentally, it has been shown that the intestinal microbiota influences lung function through communication, which is called the intestinal-pulmonary axis [4–6]. The intestinal-lung axis is most likely bi-directional, which means that the metabolites and endotoxins of the microbes can influence the state of the lower respiratory tract via the bloodstream and *vice versa* – when inflammation occurs in the lungs, the axis and this compound affect the state of the intestinal tract and microbiome [87, 88]. The loss of the diversity or quantity of intestinal bacteria may lead to dysbiosis, which may also lead to the onset of other diseases [84]. It has been observed that in immunocompromised elderly patients, abnormal clinical trial results occur [89, 90]. Therefore, it can be assumed that in the case of COVID-19, there is a possibility of mutual communication between the lung and gut microbiota, which may affect the outcome of treatment and manifest itself in various clinical pictures. The gut microbiome may play a key role in maintaining the optimal functioning of the immune system, protecting the body against overly exaggerated immune responses that ultimately damage the lungs and other anatomical parts of the lower respiratory tract [84, 89, 91].

Different forms of nutrition have been shown to influence specific patterns of intestinal tract composition. The studies showed a different composition of the microbiome in foods based on animal fats and proteins, compared to the microbiome identified by subjects on a vegetable diet [89, 91]. Both prebiotics and probiotics are included in the quantitatively and qualitatively balanced diet [91].

Prebiotic substances are components in foods that stimulate the growth or activity of bacteria in the large intestine that are beneficial to the body without digestion. These are mainly soluble and insoluble fibre fractions, as well as polyols, frutooligosaccharides and galactooligosaccharides. Some polyphenols and fatty acids are also prebiotic substances. Unlike digestible carbohydrates, indigestible carbohydrates such as fibre and resistant starch ferment. Fibre is a good source of energy for biota, which is reflected in the function of enterocytes, membrane integrity and GALT. *In vitro* studies showed that galactooligosaccharides (GOS) and arabinoxylate increased the production of IFN-γ in T helper cells 1, while the synthesis of TNF-α decreased. Studies have also confirmed that prebiotic compounds, such as inulin, polydextrose and corn fibres, support the anti-inflammatory pathways of the immune system, increase intestinal biodiversity and improve digestion in humans, with a particular focus on the elderly [92–95].

Consumption of indigestible carbohydrates in whole grain products (both soluble and insoluble fibre) has been shown to reduce the inflammatory cytokine IL-6 and insulin resistance [94–96]. Similarly, increased levels of the anti-inflammatory cytokine IL-10 were observed in plasma after ingestion of butyrylate maize starch with a high amylose content [94, 95]. Prebiotics have an indirect effect on the immune system, mainly by increasing the production of short-chain fatty acids (SCFA) and strengthening the gastrointestinal integrity of lymphatic tissue (GALT). Studies have shown that a diet rich in fibre not only changes the gut microbiome, but can also influence the lung microbiota, indicating the effects of diet on lung function [95]. Another example of the positive effect of prebiotics on the immune defense are yamsaccharides (Chinese yams, Discorea batatus), which have immunomodulatory functions and support the immune defense [96]. It is proposed that polysaccharides of liquorice (glycyrrhiza) may activate the immune system by promoting the proliferation, maturation and differentiation of lymphocytes and macrophages, as well as the reticuloendothelial system [97, 98]. Figure 1 shows the combination of all dietary components that influence the course of COVID-19 immunomodulatory.

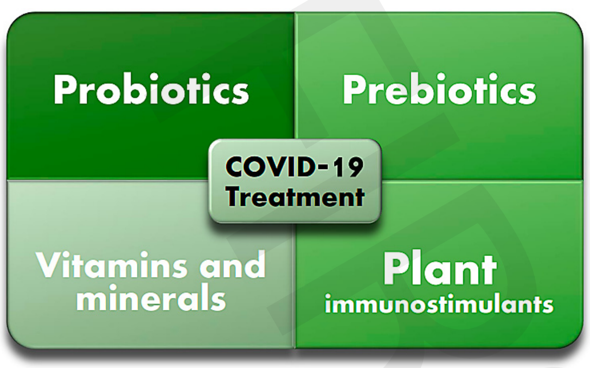

Figure 1. Table of immunomodulatory components in the diet

Fibre stimulates the growth of bacteria that are commonly regarded as commensals, such as *Bifidobacterium* and *Lactobacillus* spp. A daily intake of at least 25 g of fibre has a positive effect on the growth of the above-mentioned microorganisms, and at the same time reduces potential pathogens such as *Clostridium* spp.

Prebiotics as a breeding ground for microorganisms are closely linked to the growth and effect of probiotics. Intestinal microbes degrade various prebiotics such as fructan, glucan, arabinoxylate. The end products of intestinal fibre metabolism, short-chain fatty acids (SCFA), have been shown to have a regulatory effect on the immunity of the host. SCFAs participate in the immune response of the host via different receptors and differ in the intensity of activation of G-protein conjugated receptors (GPCRS). Some of the most important SCFAs, butyric acid and propionic acid, resulting from the fermentation of prebiotics by intestinal microbiota, may impair the differentiation and/or function of T cells, macrophages and dendritic cells. Butyrate and propionate have a direct influence on the function of B cells. Short-chain fatty acids act as HDAC inhibitors and can weaken the antibody mediated T-dependent and T-independent antibody reaction mechanisms, both intestinal and systemic [97]. This is crucial for stimulating or suppressing the immune response.

Acetate is a fermentation product for most intestinal bacteria, while butyrate and propionate are produced by more specific types of bacteria. The bacterial families of the order Clostridiales are able to produce buttermilk: Lachnospiraceae, Ruminococcaceae and Erysipelotrichaceae. A change in relative size between different types can lead to chronic inflammation [96, 97]. Among them, an increased number of *Proteobacteria* may intensify chronic and systemic inflammation, leading to increased intestinal permeability and systematic inflammation in the host, resulting in decreased immunity [96–98].

The author proposes that the improvement of the general state of the immune system can begin with the introduction of probiotics which, when integrated into individual niches, lead to reconstitution in the microbiotic, then guarantee the integrity of the intestinal wall and indirectly influence the functioning of the immune system. As has been shown in numerous studies, lactic acid rods and their fermentation products can inhibit the toxins produced by intestinal pathogens or non-comensal bacteria, and promote the health of the host [95, 97]. *Lactobacillus acidophilus*, together with other species and certain bacterial strains, has also been shown to colonize the surface of the human intestine and to have a particularly beneficial health benefit by inhibiting inflammatory cytokines. Homeostasis can be achieved by keeping a relative number of bacteria belonging to *Bacteroidetes*, *Firmicutes*, *Proteobacteria* and *Acinobacteria*. One of the tasks with direct practical implications is the use of probiotics with known immunomodulatory and anti-inflammatory mechanisms to achieve body homeostasis and inhibit the growth of pathogenic microorganisms [95, 97, 98].

CONCLUSIONS

The immunomodulatory substances discussed in this study act on various effector mechanisms of the immune response, limiting the development of the inflammatory reaction, and therefore they can potentially reduce the risk of a cytokine storm characteristic of COVID-19. Vitamin D_3 and selenium deficiency, common in patients with respiratory tract infections, and compensated with vitamin D_3 supplementation, significantly reduced the risk of respiratory tract infections. In turn, deficiencies of vitamins C, E and zinc weaken the immune system, thus leading to greater susceptibility to infections. Infection with SARS-CoV-2 led to the depletion of vitamin A stores; hence, its supplementation is suggested, while low iron levels have been correlated with the occurrence of severe symptoms in the course of COVID-19. In addition, during COVID-19 therapy, it is worth considering supplementing natural products or their derivatives, such as aloe, garlic, ginger, purple echinacea or turmeric as potential sources of immunomodulatory substances that have a beneficial effect on the treatment process of COVID-19 patients. The need should be emphasized for further scientific research on the mechanisms of action and effectiveness of phytotherapy in confirming the effectiveness of plant immunostimulants in the course of COVID-19. It is also worth considering the supply of probiotic strains in anti-covid therapy, which, by affecting the integrity of the intestinal wall, ensure the proper functioning of the body's immune system.

Natural immunomodulators may be a relatively safe therapeutic option in patients in the course of COVID-19, but there are still no official recommendations for their practical use in therapy.

Conflict of interest

The authors declare no conflict of interest.

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