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ПЕРСПЕКТИВЫ СОЗДАНИЯ НОВЫХ ЛЕЧЕБНО-ПРОФИЛАКТИЧЕСКИХ СРЕДСТВ НА ОСНОВЕ СИМБИОТИЧЕСКИХ ШТАММОВ БАКТЕРИЙ ДЛЯ КОРРЕКЦИИ НАРУШЕНИЙ ИММУННОЙ РЕГУЛЯЦИИ, ОПОСРЕДОВАННОЙ КИШЕЧНОЙ МИКРОБИОТОЙ ПРИ COVID-19

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PROSPECTS OF CREATING NEW THERAPEUTIC AND PROPHYLACTIC REMEDIES BASED ON SYMBIOTIC BACTERIAL STRAINS FOR CORRECTION OF IMMUNE REGULATION DISORDERS, MEDIATED BY INTESTINAL MICROBIOTA IN COVID-19

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Резюме

Современные исследования роли кишечной микробиоты у животных и человека показывают, что микроорганизмы является важным фактором, определяющим здоровье хозяина и участвуют в патогенезе различных инфекционных и неинфекционных заболеваний. В настоящее время активно исследуются механизмы формирования функциональной оси «кишечник-легкие» при новой коронавирусной инфекции COVID-19, где желудочно-кишечный тракт может являться входными воротами инфекции, указывая на вовлечение кишечной микробиоты в инфекционный процесс. С одной стороны, изменение микробиоты пациентов (дисбиоз), инфицированных вирусом SARS-CoV-2, является одним из факторов развития вторичной бактериальной инфекции, сепсиса, системного воспаления и полиорганной недостаточности. С другой стороны, нарушение микробиоты кишечника способствует развитию тяжелого течения и летального исхода у пациентов из-за двунаправленной связи кишечной микробиоты через систему иммунитета посредством цитокинов. Показана связь степени тяжести COVID-19 у пациентов с уровнем цитокинов и выявлением в кишечном биотопе определенных видов «провоспалительных» или «противовоспалительных» бактерий. Иммунологические нарушения у пациентов с COVID-19 также опосредованы изменением профиля метаболома на фоне дисбиотических нарушений микробиоты. Связь между составом микробиоты кишечника, уровнями цитокинов и воспалительными маркерами позволяет предположить, что микробиом кишечника влияет на развитие и течение коронавирусной инфекции, а «симбиотический потенциал» нормобиоты может быть использован для разработки мер профилактики и реабилитации пациентов. Этому может способствовать развитие исследований в направлении проблемы симбиоза человека и микробиоты. Ряд ключевых механизмов изучения интеграции бифидобактерий и лактобацилл с хозяином, опосредованные системой иммунитета, гормонов и нейромедиаторов, открывают новые перспективы для медицины, включая получение новых пробиотических штаммов различной целевой установки для лечебно-профилактической коррекции нарушенных функций организма. Изучение микросимбиоценоза, как одного из векторов ассоциативного симбиоза, позволило разработать метод межмикробного распознавания «свой-чужой», где в качестве тестовой распознающей культуры используются бифидобактерии, т.к. для «своих» штаммов характерен синергизм (поддержка), тогда как при встрече с «чужой клеткой» - антагонизм. Именно этот фундаментальный механизм можно использовать при отборе «своих» для хозяина штаммов, пригодных для создания пробиотической композиции.

Ключевые слова: COVID-19; микробиота; ось «кишечник-легкие»; симбиоз; бифидобактерии; иммунный ответ; пробиотики.

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Abstract

Modern studies of the role of the intestinal microbiota in animals and humans show that microorganisms are an important determinant of host health, participating in the pathogenesis of various infectious and non-infectious diseases. Currently, the mechanisms of formation of the functional gut-lung axis in the new coronavirus COVID-19 infection are being actively investigated. The gastrointestinal tract may be the point of entry for infection, indicating the involvement of the intestinal microbiota in the infectious process. On the one hand, changes in the microbiota (dysbiosis) in SARS-CoV-2 patients is one of the factors contributing to the development of secondary bacterial infection, sepsis, systemic inflammation and multi-organ failure. On the other hand, impaired gut microbiota contributes to the development of severe course and mortality in patients due to bidirectional coupling of the gut microbiota through the immune system via cytokines. The studies have shown a link between the severity of COVID-19 in patients with the level of cytokines and the presence of particular types of “pro-inflammatory” and “anti-inflammatory” bacteria in the intestinal biotope. Immunological abnormalities in COVID-19 patients are also mediated by metabolome profile alteration associated with dysbiotic microbiota disturbances. The connection between the composition of the gut microbiota, cytokine levels and inflammatory markers suggests that the gut microbiome influences the progression of coronavirus infection, and the "symbiotic potential" of the normobiotic microbiota can be used to develop prevention and rehabilitation measures for patients. This can be facilitated by the development of research towards the problem of human-microbiota symbiosis. A number of key mechanisms for studying the integration of bifidobacteria and lactobacilli with the host, mediated by the system of immunity, hormones and neurotransmitters, open new perspectives for medicine, including obtaining new probiotic strains of different targeting for therapeutic and preventative correction of impaired functions of the organism. The study of microsymbiocenosis as one of the vectors of associative symbiosis has enabled the development of a method of intermicrobial “friend or foe identification”, where bifidobacteria are used as a diagnostic culture, since “friendly” strains are characterised by synergism (support), whereas encountering a "foreign cell" leads to antagonism. This fundamental mechanism may be used for choosing the “host-friendly” bacteria strains eligible for the creation of a probiotic composition.

Keywords: COVID-19; microbiota; gut-lung axis; symbiosis; bifidobacteria; immune response; probiotics.

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1 Introduction

The emergence of the new COVID-19 coronavirus infection has posed the problems connected to quick diagnostics and provision of health care to patients. Currently, intensive study of the clinical and epidemiological features of the disease and the development of new means of its prevention and treatment continues. In this regard, it is of interest to discuss the role of microbiota in the new COVID-19 coronavirus infection and the possibility of using symbiotic relations between humans and microbiota in the development of therapeutic and preventative measures.

The relation of patients' gut microbiota with new COVID-19 coronavirus infection. Currently, the association of the gut microbiota with various human pathologies is receiving particular attention from researchers [20, 61, 62] due to the COVID-19 pandemic. A number of recent publications indicate that the severity of the course and consequences of COVID-19 are associated with the intestinal microbiota of infected patients [2, 16, 71].

SARS-CoV-2 virus can travel from the lungs to gastrointestinal biotopes [58]. It was found that coronavirus RNA was detected not only in respiratory secretions but also in the faeces of patients for more than one month after the onset of the disease [75]. In addition to acute respiratory syndrome, many patients with COVID-19 had extrapulmonary manifestations (nausea, vomiting, loss of appetite, diarrhoea) [14, 63], liver dysfunction and exacerbation of chronic inflammatory bowel disease [32]. Moreover, in some cases, signs of intestinal disorders in patients appeared even before pneumonia was detected [42].

The gastrointestinal tract is thought to play a key role in the development of infection, in particular through higher expression of ACE2 receptors on intestinal enterocytes compared to lung tissue cells [28, 40, 57, 76]. The binding of the virus to human ACE2 indicates that significant amounts of SARS-CoV-2 virus capable of regulating amino acid transport, affecting the quantitative and qualitative composition of the intestinal microbiota and inducing inflammation may be present in the intestine, especially in colonocytes [30, 64]. All this confirms that the gastrointestinal tract may be the point of entry of infection and indicates the involvement of the intestinal microbiota in the infectious process in the new COVID-19 coronavirus infection and the formation of a functional gut-lung axis [4, 65]. The link between the gastrointestinal tract and the respiratory tract has also been shown in studies on the effect of respiratory viral infections on the composition of the intestinal microbiota with the subsequent development of intestinal dysbiosis [27]. Thus, patients with COVID-19 had significant microecological disorders in the large intestine compared to the control group, characterised by an increase in the proportion of opportunistic microorganisms associated with a decrease in the level of representatives of normal microbiota [21, 74]. It is noted that the composition of the gut microbiome was significantly altered in patients with COVID-19 compared to patients without the coronavirus infection, regardless of whether they were taking medication. Gut dysbiosis persisted even after SARS-CoV-2 was eliminated, and

respiratory symptoms disappeared. A pilot study by Chinese scientists found changes in the gut microbiome in patients with COVID-19 compared with the control group, characterised by an increase in the number of fungal pathogens of the genus Candida and Aspergillus [3, 82].

To date, disruption of the gut microbiota is thought to contribute to the severe course and fatal outcome of novel COVID-19 coronavirus infection because of the bidirectional coupling of the gut microbiota with the immune and respiratory systems [3]. The formation of microecological disorders leads to increased permeability of the large intestine and, as a consequence, appears to be one of the factors in the development of secondary bacterial infection, sepsis, systemic inflammation and multi-organ failure [24, 52, 56]. Large intestinal dysbiosis has also been found to be associated with various chronic human conditions such as asthma, arthritis, obesity and type 2 diabetes [4, 31, 67]. Previously, bacterial translocation from the gut to the lungs has been identified in sepsis and acute respiratory distress syndrome [17].

Immune regulation impairment mediated by intestinal microbiota in COVID-19. Changes in the microbiota of patients infected with SARS-CoV-2 virus are naturally accompanied by immunological rearrangements and the suppression of T-cell immunity [66, 81]. A number of researchers have shown a correlation between the severity of COVID-19 in patients and the level of cytokines, which, in turn, have been associated with the detection of certain types of "pro-inflammatory" or "anti-inflammatory" bacteria in the intestinal biotope [37, 43, 46, 51, 78], confirming the role of the microbiota in immune dysregulation. The composition of patients' gut microbiota has been found to be associated with plasma concentrations of aspartate aminotransferase (AST), chemokine receptor (CXCL10), CRP and lactate dehydrogenase (LDH) [78]. On the other hand, the induction of mediators of the inflammatory cascade further aggravates gut dysbiosis by disrupting the immune homeostasis of the biotope and the relationship between the resident microbiota and the gut immune system, leading to excessive pathological inflammation or chronic inflammatory diseases. This is supported by a study of blood samples from COVID-19 patients which showed a correlation between gut dysbiosis, the increased quantity of inflammatory mediators and the severity of systemic inflammation [5, 36, 78].

Immunological disorders in patients with COVID-19 are also mediated by changes in the metabolome profile that occur naturally against the background of dysbiotic microbiota disorders [19]. Short-chain fatty acids (SCFAs), bile acids, amino acids, carbohydrates, and neurotransmitters are known to be among the significant immunoregulatory metabolites of the microbiota [34, 48]. Recent studies have demonstrated the ability of butyrate produced by the gut microbiota to affect the membrane receptor ACE2, inactivate viral spike protein and inhibit SARS-CoV-2 virus replication [41]. A decrease in or disappearance of butyrate-producing bacteria in the biotope, along with an increase in pro-inflammatory mediators (C-reactive protein, IL-6 and sIL2R), has been found in patients in severe and critical conditions

[59]. Other studies have shown the ability of ursodeoxycholate produced by bacteria of the genus Collinsella to block virus attachment to ACE2 receptors [53] and inhibit pro-inflammatory cytokines [38], preventing the development of cytokine storm [1]. The blocking of cytokine storm was also found on the model of Bacteroidetes bacteria through inhibition of toll-like receptor 4 (TLR4) and signalling pathways related to the ACE2 receptor [22, 70]. The disruption of the biosynthesis of SCFAs and L-isoleucine, associated with high levels of CRP and CXCL10 in plasma, was attributed to the disappearance of the bacterium Faecalibacterium prausnitzii [44, 77, 79]. It was found that amino acids produced by bacteria were positively correlated with high levels of pro-inflammatory cytokines (CXCL9, CXCL10, IFN-γ and IL-6) and negatively correlated with low levels of cytokines IL-9 and IL-17 in COVID-19. The content of biogenic amines had a positive correlation with low levels of cytokines CCL22, IL-12 and IL-13, but negatively correlated with high levels of pro-inflammatory cytokines (IL-6 and IL-10) [48]. Other microbial neurotransmitters such as tryptophan and polygammaglutamic acid (gamma-PGA) stimulated dendritic cells to polarise CD4+ cells towards Th1 [29].

Giron LB et al (2021) found a decrease in citrulline (a marker of intestinal function), an increase in succinic acid (a marker of dysbiosis) and an increase in the kynurenine/tryptophan ratio in severe COVID-19. Citrulline was inversely correlated with IL-6, while succinic acid level and kynurenine/tryptophan ratio were positively correlated with IL-6 concentration [25].

Disruption of intestinal barrier integrity is considered to be one of the key inducers of systemic inflammation in COVID-19, as it promotes translocation of microbial cells or their components into the systemic bloodstream and stimulation of proinflammatory cytokine secretion, and may lead to the development of a cytokine storm [55, 72]. Lipopolysaccharides (LPS), peptidoglycan (PGN), zonulin, β-glucan and lipopolysaccharide binding protein (LBP) have been found to be indicators of intestinal barrier dysfunction in the plasma of COVID-19 patients associated with the regulation of immune response [25]. It is known that zonulin, β-glucan and LBP are positively correlated with factors of systemic inflammation and immune activation, including CRP, IL-6 and IL-10. In addition, increased permeability and microbial translocation may contribute to microbiota-mediated myeloid inflammation. As expected, levels of monocyte and neutrophil inflammatory markers (soluble CD14 (sCD14) and myeloperoxidase (MPO)) were elevated in the group of patients with severe COVID-19 compared to the group of patients with mild COVID-19 and the control group. In addition, plasma concentrations of pro-inflammatory cytokines IFN-γ, IL-6, IL-8, MCP-1, macrophage inflammatory protein (MIP)-1α, MIP-1β, and TNF-α were elevated in COVID-19 patients [55].

Role of normal microbiota in the formation of biotope immune homeostasis. It is known that the physiological role of the gut microbiota, and, first of all, of the normal microbiota (bifido- and lactobacilli) is largely related to the ability of prokaryotes to regulate the development and function of the innate and adaptive

human immune system [49]. Intestinal microsymbionts influence the secretion of antimicrobial peptides, pro- and anti-inflammatory cytokines, compete for nutrients and habitat, thus contributing to the maintenance of homeostasis [47]. One of the mechanisms of microbiota immune regulation is the ability to influence the production of a certain type of regulatory molecules - cytokines as growth factors and stimulation/suppression of their synthesis [15,39]. Some pathogenic and opportunistic bacteria secrete enzymes that allow microorganisms to cleave basic types of organic macromolecules. It is known that signalling molecules of the intestinal microbiota (short-chain fatty acids such as butyrate, acetate, propionate, and secondary bile acids) are able to regulate pro- and anti-inflammatory responses in the human body [50]. Immune homeostasis of the intestine is regulated by T-reg cells which are ultimately controlled by members of the normal human microbiota (bifido- and lactobacilli) through the toll-like receptor (TLR) system and nucleotide binding receptors (NOD) [60]. Inactivation of cytokines (antipeptide activity) [3], which are the product of activated T-lymphocytes, macrophages, dendritic cells, may entail significant disturbances in the mechanisms of innate and adaptive immunity. The balance of these regulatory molecules is important for human homeostasis, as cytokines participate in the regulation of the immune response during infection [12]. The production of cytokines in response to the presence of microorganisms implies not only indirect (through the regulation of immunity), but also direct contact of bacteria with these signalling molecules. This fact has significance in the development of complications in the new COVID-19 coronavirus infection, since one of the mechanisms of pathogenesis is the generation of a cytokine storm. The excessive immune response to the virus (cytokine storm) eventually causes multi-organ failure and patient mortality; therefore, a balanced immune response is needed, where an over- or under-reactive immune system response may equally exacerbate complications such as pneumonia and ARDS in new COVID-19 coronavirus infection. Healthy gut microbiome may be critical for maintaining optimal immune system function.

The management of microecological disorders of intestinal microbiota via bifidobacteria and lactobacilli normalises immune reactions and may be one of the ways to prevent complications, as well as reduce the risks of SARS-CoV-2 disease. Thus, administration of probiotic strains such as Bifidobacterium lactis to healthy elderly volunteers resulted in a significant increase in the proportion of mononuclear leukocytes and NK cells [23]. It is known that the composition of intestinal microbiota, primarily normobiota (bifido- and lactobacilli), has a great influence on the effectiveness of pulmonary immunity [6]. Animal experiments have shown that the ability to eliminate pathogens in the lungs was impaired in mice deprived of gut microbiota [18]. Disruption of the gut microbiota (dysbiosis) by the widespread use of antibiotics may also have an effect similar to that observed in population studies showing that inappropriate and uncontrolled use of antibacterial drugs such as penicillins, cephalosporins, macrolides and quinolones correlates with an increased risk of lung cancer in humans [7].

The use of probiotic medicines based on Lactobacillus and Bifidobacterium cultures has demonstrated positive results in the realisation of anti-inflammatory and immunoregulatory response of the organism [73]. It was found that the administration of some strains of probiotic bacteria (*Lacticaseibacillus rhamnosus*, *Bifidobacterium lactis* and *Bifidobacterium breve*) to experimental animals promotes the proliferation of T-reg-lymphocytes, suppressing inflammatory and allergic reactions in the organism [20], and administration of lactobacilli (*Lacticaseibacillus casei Shirota* or *Lacticaseibacillus rhamnosus GG*) to patients with cystic fibrosis leads to improvement of their condition [73].

Prospects for the development of targeted probiotics. It is now assumed that probiotic bacteria can be used for preventative or therapeutic purposes of inducing hormonal and immune changes in the body, since the participation of normobiotics (on the model of lactobacilli) in the regulation of the production of the neuropeptide hormone, oxytocin, has been proved [54, 69]. These studies are of interest because oxytocin is considered to be one of the possible candidates for the treatment of COVID-19. Oxytocin is known to be able to exert a dual action: to mobilise the immune defence potential and suppress excessive reactions of innate immunity, to limit pro-inflammatory (cytokine storm) and oxidative stress reactions by reducing cytokine levels. It has been suggested that even if oxytocin does not have a direct antiviral action, it still has sufficient mechanisms that may make it effective against COVID-19 through immunomodulatory, cardioprotective, antidiabetic and anabolic functions [35]. A number of studies have shown that some strains of normobiota (living cells and their components) are able to stimulate oxytocin and have immunoregulatory activity [54].

Of particular interest for COVID-19 treatment and prevention is nitric oxide (NO), which is a key signalling molecule that acts as a modulator of the host response in viral infections [68, 80]. At the same time, the microbiota is one of the sources of nitric oxide production directly [45] or indirectly through the induction of immune cells [10].

One of the problems arising in the use of biological medicines (synbiotics, probiotics, etc.) is the gradual decrease in the level of their antagonistic activity [11, 26], which ultimately affects the therapeutic and preventive efficacy of drugs. Also, one of the reasons for the low levels of effectiveness or its absence of probiotics is their foreignness to microorganisms [13]. Currently, as an alternative, for the correction of human dysbiosis, it is proposed to use one’s own strains of bifidobacteria (autostrains), that are biocompatible, due to which they effectively form a biofilm with other representatives of the indigeneous microbiota under the conditions of microsymbiocenosis, in contrast to industrial strains of bacteria, which are not always able to colonise the human intestine [33].

When creating a consortium of microorganisms of probiotic action, bacterial strains are also selected without taking into account their biocompatibility in the

composition, which can lead to suppression of microorganism viability and loss of their practically significant properties.

Two described biological universal phenomena of a fundamental nature contribute greatly to the solution of these problems: 1) associative symbiosis [9]; 2) bacterial persistence [8].

The study of microsymbiocenosis as one of the vectors of associative symbiosis allowed developing a method of intermicrobial “friend or foe” identification, where bifidobacteria are used as a diagnostic culture, since “friendly” strains are characterised by synergism (support), whereas encountering a “foreign cell” leads to antagonism. This fundamental mechanism may be used for choosing the “host-friendly” bacteria strains eligible for the creation of a probiotic composition. In this regard, one of the priority directions in the design of microbial compositions of pro- and synbiotics may be the use of the phenomenon of microbial “friend or foe” identification, which has proven itself well for the assessment of foreignness of *E. coli* strains [12].

As for another fundamental phenomenon, persistent potential of bacteria which fulfils the role of a "microbial biotarget", these adaptation characteristics may be used to solve an equally important task, the assessment of biocompatibility of microbial cultures, since preliminary studies have shown their full suitability for the specified purpose. Based on the method of intermicrobial identification, the principle of biocompatibility of probiotic cultures of microorganisms was formulated based on the oppositional (amplification/suppression) phenomenon of regulatory relations of microsymbionts, where it is possible to apply quantitative determination of the degree of biocompatibility of cultures based on the adaptive potential (biofilm formation and anti-lysozyme test) of bacteria. Such a two-in-one combination - inclusion of biocompatibility assessment of microsymbionts with simultaneous determination of “friend-foe” - can form the basis for selection of probiotic strains and formation of new drug compositions based on them [10, 12].

2 **Conclusion**

Thus, modern studies of the role of intestinal microbiota in animals and humans show that the intestinal microbiota is an important factor determining health, influencing immunity, participating in the pathogenesis of various infectious and non-infectious diseases. The pronounced contribution of the intestinal microsymbiocenosis is realised through the maintenance of a number of physiological functions and the formation of homeostasis of the host organism. The association between gut microbiota composition, cytokine levels and inflammatory markers in COVID-19 patients suggests that the gut microbiome influences the severity of the course of coronavirus infection. A number of key mechanisms for studying the integration of bifidobacteria and lactobacilli with the host, mediated by the system of immunity, hormones and neurotransmitters, open new perspectives for medicine, including obtaining new probiotic strains of different targeting for therapeutic and prophylactic correction of disturbed body functions.

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Блок 3. Метаданные статьи

ПЕРСПЕКТИВЫ СОЗДАНИЯ НОВЫХ ЛЕЧЕБНО-ПРОФИЛАКТИЧЕСКИХ СРЕДСТВ НА ОСНОВЕ СИМБИОТИЧЕСКИХ ШТАММОВ БАКТЕРИЙ ДЛЯ КОРРЕКЦИИ НАРУШЕНИЙ ИММУННОЙ РЕГУЛЯЦИИ, ОПОСРЕДОВАННОЙ КИШЕЧНОЙ МИКРОБИОТОЙ ПРИ COVID-19

PROSPECTS OF CREATING NEW THERAPEUTIC AND PROPHYLACTIC REMEDIES BASED ON SYMBIOTIC BACTERIAL STRAINS FOR CORRECTION OF IMMUNE REGULATION DISORDERS, MEDIATED BY INTESTINAL MICROBIOTA IN COVID-19

Сокращенное название статьи для верхнего колонтитула:
ПРОБИОТИКИ КАК ИММУННЫЕ РЕГУЛЯТОРЫ ПРИ COVID-19
PROBIOTICS AS IMMUNE REGULATORS FOR COVID-19

Ключевые слова: COVID-19; микробиота; ось «кишечник-легкие»; симбиоз; бифидобактерии; иммунный ответ; пробиотики.
Keywords: COVID-19; microbiota; gut-lung axis; symbiosis; bifidobacteria; immune response; probiotics.

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СПИСОК ЛИТЕРАТУРЫ

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1	Abdulrab S, Al-Maweri S, Halboub E. Ursodeoxycholic acid as a candidate therapeutic to alleviate and/or prevent COVID-19-associated cytokine storm. Med Hypotheses. 2020 Oct;143:109897.	DOI: 10.1016/j.mehy.2020.109897
2	Ahlawat S, Asha, Sharma KK. Immunological co-ordination between gut and lungs in SARS-CoV-2 infection. Virus Res. 2020 Sep;286:198103.	doi: 10.1016/j.virusres.2020.198103
3	Aktas B, Aslim B. Gut-lung axis and dysbiosis in COVID-19. Turk J Biol. 2020 Jun 21;44(3):265-272.	doi: 10.3906/biy-2005-102.
4	Aleman FDD, Valenzano DR (2019) Microbiome evolution during host aging. PLoS Pathog 15(7): e1007727.	https://doi.org/10.1371/journal.ppat.1007727
5	Belkaid Y, Harrison OJ. Homeostatic immunity and the microbiota. Immunity (2017) 46(4):562–76.	DOI: 10.1016/j.immuni.2017.04.008
6	Bingula R, Filaire M, Radosevic-Robin N, Bey M, Berthon JY, Bernalier-Donadille A, Vasson MP, Filaire E. Desired Turbulence? Gut-Lung Axis, Immunity, and Lung Cancer. J Oncol. 2017;2017:5035371.	DOI: 10.1155/2017/5035371
7	Boursi B, Mamtani R, Haynes K, Yang YX. Recurrent antibiotic exposure may promote cancer formation--Another step in	DOI: 10.1016/j.ejca.2015.08.015

ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

	understanding the role of the human microbiota? Eur J Cancer. 2015 Nov;51(17):2655-64.	
8	Bukharin O.V. Persistence of pathogenic bacteria. Moscow: Meditsina, 1999. 365 p.	
9	Bukharin O.V., Lobakova E.S., Nemtseva N.V., Cherkasov S.V. Associative symbiosis. Ekaterinburg; UD RAS 2007. 264 p.	
10	Bukharin O.V., Perunova N.B., Ivanova E.V. Bifidoflora in human associative symbiosis. Ekaterinburg: UrD of the RAS, 2014. 212 p.	
11	Bukharin O. V., Semenov A. V., Cherkasov S.V. Antagonistic activity of probiotic bacteria. Clinical Microbiology and Antimicrobial Chemotherapy. 2010; 12 (4): 347-352.	https://cmac-journal.ru/en/publication/2010/4/
12	Bukharin O.V., Stadnikov A.A., Perunova N.B. Oxytocin and microbiota role in regulation of pro- and eukaryote interactions in infection. Ekaterinburg: UrD of the RAS, 2018. 247 p.	
13	Chervinets Yu.V., Cervinets V. M., Mironov A. Yu. Symbiotic relationships of lactobacilli and microorganisms of the gastrointestinal tract. Tver. Center. Tver state medical university Publ., 2016. 214 p	
14	Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong	DOI: 10.1053/j.gastro.2020.03.065

ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

	Cohort: Systematic Review and Meta-analysis. Gastroenterology. 2020 Jul;159(1):81-95.	
15	Chung H, Pamp SJ, Hill JA, Surana NK, Edelman SM, Troy EB, et al. Gut immune maturation depends on colonization with a host-specific microbiota. *Cell* (2012) 149(7):1578–93.	DOI: 10.1016/j.cell.2012.04.037
16	Dhar D, Mohanty A. Gut microbiota and Covid-19- possible link and implications. Virus Res. 2020 Aug;285:198018.	DOI: 10.1016/j.virusres.2020.198018
17	Dickson RP, Singer BH, Newstead MW, Falkowski NR, Erb-Downward JR, Standiford TJ, Huffnagle GB. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. Nat Microbiol. 2016 Jul 18;1(10):16113.	DOI: 10.1038/nmicrobiol.2016.113
18	Fagundes CT, Amaral FA, Vieira AT, Soares AC, Pinho V, Nicoli JR, Vieira LQ, Teixeira MM, Souza DG. Transient TLR activation restores inflammatory response and ability to control pulmonary bacterial infection in germfree mice. J Immunol. 2012 Feb 1;188(3):1411-20.	DOI: 10.4049/jimmunol.1101682
19	Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol. 2021 Jan;19(1):55-71.	DOI: 10.1038/s41579-020-0433-9
20	Feleszko W, Jaworska J, Rha RD, Steinhausen S, Avagyan A, Jaudszus A, Ahrens B, Groneberg DA, Wahn U, Hamelmann E. Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. Clin Exp Allergy. 2007 Apr;37(4):498-505.	DOI: 10.1111/j.1365-2222.2006.02629.x
21	Gaibani P, D'Amico F, Bartoletti M, Lombardo D, Rampelli S, Fornaro G, Coladonato S, Siniscalchi A, Re MC, Viale P, Brigidi P,	doi: 10.3389/fcimb.2021.670424.

	Turroni S, Giannella M. The Gut Microbiota of Critically Ill Patients With COVID-19. Front Cell Infect Microbiol. 2021 Jun 29;11:670424.	
22	Geva-Zatorsky N, Sefik E, Kua L, Pasman L, Tan TG, Ortiz-Lopez A, Yanortsang TB, Yang L, Jupp R, Mathis D, Benoist C, Kasper DL. Mining the Human Gut Microbiota for Immunomodulatory Organisms. Cell. 2017 Feb 23;168(5):928-943.e11.	DOI: 10.1016/j.cell.2017.01.022
23	Gill HS, Rutherfurd KJ, Cross ML, Gopal PK. Enhancement of immunity in the elderly by dietary supplementation with the probiotic Bifidobacterium lactis HN019. Am J Clin Nutr. 2001 Dec;74(6):833-9.	DOI: 10.1093/ajcn/74.6.833 .
24	Gill HS, Rutherfurd KJ, Cross ML. Dietary probiotic supplementation enhances natural killer cell activity in the elderly: an investigation of age-related immunological changes. J Clin Immunol. 2001 Jul;21(4):264-71.	DOI: 10.1023/a:1010979225018
25	Giron LB, Dweep H, Yin X, Wang H, Damra M, Goldman AR, Gorman N, Palmer CS, Tang HY, Shaikh MW, Forsyth CB, Balk RA, Zilberstein NF, Liu Q, Kossenkov A, Keshavarzian A, Landay A, Abdel-Mohsen M. Plasma Markers of Disrupted Gut Permeability in Severe COVID-19 Patients. Front Immunol. 2021 Jun 9;12:686240.	DOI: 10.3389/fimmu.2021.686240
26	Glushanova NA, Shenderov BA. [Relationships between the probiotic and host indigenous lactobacilli under the conditions of mixed cultivation in vitro]. Zh Mikrobiol Epidemiol Immunobiol. 2005 Mar-Apr;(2):56-61. Russian.	PMID: 15881941.
27	Groves HT, Cuthbertson L, James P, Moffatt MF, Cox MJ, Tregoning JS. Respiratory Disease following Viral Lung Infection Alters the Murine Gut Microbiota. Front Immunol. 2018 Feb 12;9:182.	DOI: 10.3389/fimmu.2018.00182

28	Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW. Extrapulmonary manifestations of COVID-19. Nat Med. 2020 Jul;26(7):1017-1032	DOI: 10.1038/s41591-020-0968-3
92	Haase S, Haghikia A, Wilck N, Müller DN, Linker RA. Impacts of microbiome metabolites on immune regulation and autoimmunity. Immunology. 2018 Jun;154(2):230-238.	DOI: 10.1111/imm.12933
30	Hashimoto T, Perlot T, Rehman A, Trichereau J, Ishiguro H, Paolino M, Sigl V, Hanada T, Hanada R, Lipinski S, Wild B, Camargo SM, Singer D, Richter A, Kuba K, Fukamizu A, Schreiber S, Clevers H, Verrey F, Rosenstiel P, Penninger JM. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature. 2012 Jul 25;487(7408):477-81.	DOI: 10.1038/nature11228
31	Hufnagl K, Pali-Schöll I, Roth-Walter F, Jensen-Jarolim E. Dysbiosis of the gut and lung microbiome has a role in asthma. Semin Immunopathol. 2020 Feb;42(1):75-93.	DOI: 10.1007/s00281-019-00775-y
32	Iacucci M, Cannatelli R, Labarile N, Mao R, Panaccione R, Danese S, Kochhar GS, Ghosh S, Shen B. Endoscopy in inflammatory bowel diseases during the COVID-19 pandemic and post-pandemic period. Lancet Gastroenterol Hepatol. 2020 Jun;5(6):598-606.	DOI: 10.1016/S2468-1253(20)30119-9
33	Il'in VK, Suvorov AN, Kiriukhina NV, Usanova NA, Starkova LV, Boiarintsev VV, Karaseva AB. [Autochthonous probiotics in prevention of infectious and inflammatory diseases of a human in	DOI: 10.15690/vramn.v68i2.550

ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

	the altered habitats]. Vestn Ross Akad Med Nauk. 2013;(2):56-62. Russian.	
34	Jia W, Xie G, Jia W. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. Nat Rev Gastroenterol Hepatol. 2018 Feb;15(2):111-128.	DOI: 10.1038/nrgastro.2017.119
35	Kasabri V, Shawakri E, Akour A, Naffa R, Khawaja N, Al-Sarraf I, Bzour J. Cross-sectional correlates of increased IL-18 but reduced fetuin-A and oxytocin with adiposity and blood indices in metabolic syndrome patients with and without prediabetes. Ther Adv Endocrinol Metab. 2018 Aug 18;9(12):329-338.	DOI: 10.1177/2042018818788802 .
36	Katz-Agranov N, Zandman-Goddard G. Autoimmunity and COVID-19 - The microbiotal connection. Autoimmun Rev. 2021 Aug;20(8):102865.	DOI: 10.1016/j.autrev.2021.102865 .
37	Khan M, Mathew BJ, Gupta P, Garg G, Khadanga S, Vyas AK, Singh AK. Gut Dysbiosis and IL-21 Response in Patients with Severe COVID-19. Microorganisms. 2021 Jun 13;9(6):1292.	DOI: 10.3390/microorganisms9061292
38	Koptyug A, Sukhovei Y, Kostolomova E, Unger I, Kozlov V. Novel Strategy in Searching for Natural Compounds with Anti-Aging and Rejuvenating Potential. Int J Mol Sci. 2023 Apr 28;24(9):8020.	DOI: 10.3390/ijms24098020
39	Kostolomova E.G., Timokhina T.K., Perunova N.B., et al. *In vitro* evaluation of immunomodulatory activity of *Bifidobacterium bifidum* 791 in the cell model of innate and adaptive immunity // Russian Journal of Immunology. - 2022. - Vol. 25. - N. 2. - P. 213-218.	doi: 10.46235/1028-7221-1133-IVE
40	Jabczyk M, Nowak J, Hudzik B, Zubelewicz-Szkodzińska B. Microbiota and Its Impact on the Immune System in COVID-19-A Narrative Review. J Clin Med. 2021 Sep 30;10(19):4537.	doi: 10.3390/jcm10194537

41	Li J, Richards EM, Handberg EM, Pepine CJ, Raizada MK. Butyrate Regulates COVID-19-Relevant Genes in Gut Epithelial Organoids From Normotensive Rats. Hypertension. 2021 Feb;77(2):e13-e16.	DOI: 10.1161/HYPERTENSIONAHA.120.16647
42	Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, Gu Z, Gao L, Shi H, Mai L, Liu Y, Lin X, Lai R, Yan Z, Li X, Shan H. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020 Jun;69(6):997-1001.	DOI: 10.1136/gutjnl-2020-321013
43	Litvak Y, Byndloss MX, Bäumler AJ. Colonocyte metabolism shapes the gut microbiota. Science. 2018 Nov 30;362(6418):eaat9076.	DOI: 10.1126/science.aat9076.
44	Mao X, Gu C, Ren M, Chen D, Yu B, He J, Yu J, Zheng P, Luo J, Luo Y, Wang J, Tian G, Yang Q. l-Isoleucine Administration Alleviates Rotavirus Infection and Immune Response in the Weaned Piglet Model. Front Immunol. 2018 Jul 16;9:1654.	doi: 10.3389/fimmu.2018.01654
45	Markov A.A., Kostolomova E.G., Timokhina T.Kh., Solovyev G.S., Paromova Ya.I., Polyanskih E.D., Voronin K.A. Effect of *Bifidobacterium bifidum* supernatant on the morphological and functional characteristics of human fibroblasts in real time during an *in vitro* experiment. *Medical Immunology (Russia)*. 2023;25(3):581-586.	https://doi.org/10.15789/1563-0625-EOB-2720
46	Mizutani T, Ishizaka A, Koga M, Ikeuchi K, Saito M, Adachi E, Yamayoshi S, Iwatsuki-Horimoto K, Yasuhara A, Kiyono H, Matano T, Suzuki Y, Tsutsumi T, Kawaoka Y, Yotsuyanagi H. Correlation Analysis between Gut Microbiota Alterations and the Cytokine Response in Patients with Coronavirus Disease during Hospitalization. Microbiol Spectr. 2022 Apr 27;10(2):e0168921.	DOI: 10.1128/spectrum.01689-21
47	Moens E, Veldhoen M. Epithelial barrier biology: good fences make good neighbours. Immunology. 2012 Jan;135(1):1-8.	DOI: 10.1111/j.1365-2567.2011.03506.x

48	Nagata N, Takeuchi T, Masuoka H, Aoki R, Ishikane M, Iwamoto N, Sugiyama M, Suda W, Nakanishi Y, Terada-Hirashima J, Kimura M, Nishijima T, Inooka H, Miyoshi-Akiyama T, Kojima Y, Shimokawa C, Hisaeda H, Zhang F, Yeoh YK, Ng SC, Uemura N, Itoi T, Mizokami M, Kawai T, Sugiyama H, Ohmagari N, Ohno H. Human Gut Microbiota and Its Metabolites Impact Immune Responses in COVID-19 and Its Complications. Gastroenterology. 2023 Feb;164(2):272-288.	DOI: 10.1053/j.gastro.2022.09.024
49	Negi S, Das DK, Pahari S, Nadeem S, Agrewala JN. Potential Role of Gut Microbiota in Induction and Regulation of Innate Immune Memory. Front Immunol. 2019 Oct 25;10:2441.	DOI: 10.3389/fimmu.2019.02441
50	Negi S, Pahari S, Bashir H, Agrewala JN. Gut Microbiota Regulates Mincle Mediated Activation of Lung Dendritic Cells to Protect Against *Mycobacterium tuberculosis*. Front Immunol. 2019 May 28;10:1142.	DOI: 10.3389/fimmu.2019.01142
51	Nejadghaderi SA, Nazemalhosseini-Mojarad E, Asadzadeh Aghdaei H. Fecal microbiota transplantation for COVID-19; a potential emerging treatment strategy. Med Hypotheses. 2021 Feb;147:110476.	DOI: 10.1016/j.mehy.2020.110476
52	Ostaff MJ, Stange EF, Wehkamp J. Antimicrobial peptides and gut microbiota in homeostasis and pathology. EMBO Mol Med. 2013 Oct;5(10):1465-83.	doi: 10.1002/emmm.201201773.
53	Poochi SP, Easwaran M, Balasubramanian B, Anbuselvam M, Meyyazhagan A, Park S, Bhotla HK, Anbuselvam J, Arumugam VA, Keshavarao S, Kanniyappan GV, Pappusamy M, Kaul T. Employing bioactive compounds derived from *Ipomoea obscura* (L.) to evaluate	DOI: 10.1002/fft2.29

ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

	potential inhibitor for SARS-CoV-2 main protease and ACE2 protein. Food Front. 2020 Jun;1(2):168-179	
54	Poutahidis T, Kearney SM, Levkovich T, Qi P, Varian BJ, Lakritz JR, Ibrahim YM, Chatzigiagkos A, Alm EJ, Erdman SE. Microbial symbionts accelerate wound healing via the neuropeptide hormone oxytocin. PLoS One. 2013 Oct 30;8(10):e78898.	DOI: 10.1371/journal.pone.0078898. .
55	Prasad R, Patton MJ, Floyd JL, Fortmann S, DuPont M, Harbour A, Wright J, Lamendella R, Stevens BR, Oudit GY, Grant MB. Plasma Microbiome in COVID-19 Subjects: An Indicator of Gut Barrier Defects and Dysbiosis. Int J Mol Sci. 2022 Aug 15;23(16):9141.	doi: 10.3390/ijms23169141
56	Proctor LM. The Human Microbiome Project in 2011 and beyond. Cell Host Microbe. 2011 Oct 20;10(4):287-91.	DOI: 10.1016/j.chom.2011.10.001
57	Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun. 2020 May 21;526(1):135-140.	DOI: 10.1016/j.bbrc.2020.03.044
58	Qian Q, Fan L, Liu W, Li J, Yue J, Wang M, Ke X, Yin Y, Chen Q, Jiang C. Direct Evidence of Active SARS-CoV-2 Replication in the Intestine. Clin Infect Dis. 2021 Aug 2;73(3):361-366.	DOI: 10.1093/cid/ciaa925
59	Reinold J, Farahpour F, Fehring C, Dolff S, Konik M, Korth J, van Baal L, Hoffmann D, Buer J, Witzke O, Westendorf AM, Kehrmann J. A Pro-Inflammatory Gut Microbiome Characterizes SARS-CoV-2 Infected Patients and a Reduction in the Connectivity of an Anti-Inflammatory Bacterial Network Associates With Severe COVID-19. Front Cell Infect Microbiol. 2021 Nov 17;11:747816.	DOI: 10.3389/fcimb.2021.747816

ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

60	Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol. 2009 May;9(5):313-23.	DOI: 10.1038/nri2515
61	Saad MJ, Santos A, Prada PO. Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. Physiology (Bethesda). 2016 Jul;31(4):283-93.	DOI: 10.1152/physiol.00041.2015
62	Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V, Chesselet MF, Keshavarzian A, Shannon KM, Krajmalnik-Brown R, Wittung-Stafshede P, Knight R, Mazmanian SK. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. Cell. 2016 Dec 1;167(6):1469-1480.e12.	DOI: 10.1016/j.cell.2016.11.018
63	Sarkesh A, Daei Sorkhabi A, Sheykhsaran E, Alinezhad F, Mohammadzadeh N, Hemmat N, Bannazadeh Baghi H. Extrapulmonary Clinical Manifestations in COVID-19 Patients. Am J Trop Med Hyg. 2020 Nov;103(5):1783-1796.	DOI: 10.4269/ajtmh.20-0986
64	Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020 May;581(7807):221-224.	DOI: 10.1038/s41586-020-2179-y
65	Song Y, Liu P, Shi XL, Chu YL, Zhang J, Xia J, Gao XZ, Qu T, Wang MY. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. Gut. 2020 Jun;69(6):1143-1144.	DOI: 10.1136/gutjnl-2020-320891
66	Sun Z, Song ZG, Liu C, Tan S, Lin S, Zhu J, Dai FH, Gao J, She JL, Mei Z, Lou T, Zheng JJ, Liu Y, He J, Zheng Y, Ding C, Qian F, Zheng Y, Chen YM. Gut microbiome alterations and gut barrier dysfunction	DOI: 10.1186/s12916-021-02212-0

ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

	are associated with host immune homeostasis in COVID-19 patients. BMC Med. 2022 Jan 20;20(1):24	
67	Tai N, Wong FS, Wen L. The role of gut microbiota in the development of type 1, type 2 diabetes mellitus and obesity. Rev Endocr Metab Disord. 2015 Mar;16(1):55-65.	DOI: 10.1007/s11154-015-9309-0
68	Thibonnier M, Conarty DM, Preston JA, Plesnicher CL, Dweik RA, Erzurum SC. Human vascular endothelial cells express oxytocin receptors. Endocrinology. 1999 Mar;140(3):1301-9.	DOI: 10.1210/endo.140.3.6546
69	Varian BJ, Poutahidis T, DiBenedictis BT, Levkovich T, Ibrahim Y, Didyk E, Shikhman L, Cheung HK, Hardas A, Ricciardi CE, Kolandaivelu K, Veenema AH, Alm EJ, Erdman SE. Microbial lysate upregulates host oxytocin. Brain Behav Immun. 2017 Mar;61:36-49.	DOI: 10.1016/j.bbi.2016.11.002
70	Vatanen T, Kostic AD, d'Hennezel E, Siljander H, Franzosa EA, Yassour M, Kolde R, Vlamakis H, Arthur TD, Hämäläinen AM, Peet A, Tillmann V, Uibo R, Mokurov S, Dorshakova N, Ilonen J, Virtanen SM, Szabo SJ, Porter JA, Lähdesmäki H, Huttenhower C, Gevers D, Cullen TW, Knip M; DIABIMMUNE Study Group; Xavier RJ. Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans. Cell. 2016 May 5;165(4):842-53.	DOI: 10.1016/j.cell.2016.04.007
71	Viana SD, Nunes S, Reis F. ACE2 imbalance as a key player for the poor outcomes in COVID-19 patients with age-related comorbidities - Role of gut microbiota dysbiosis. Ageing Res Rev. 2020 Sep;62:101123.	doi: 10.1016/j.arr.2020.101123
72	Wang B, Zhang L, Wang Y, Dai T, Qin Z, Zhou F, Zhang L. Alterations in microbiota of patients with COVID-19: potential	DOI: 10.1038/s41392-022-00986-0

ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

	mechanisms and therapeutic interventions. Signal Transduct Target Ther. 2022 Apr 29;7(1):143.	
73	West CE, Dzidic M, Prescott SL, Jenmalm MC. Bugging allergy; role of pre-, pro- and synbiotics in allergy prevention. Allergol Int. 2017 Oct;66(4):529-538.	DOI: 10.1016/j.alit.2017.08.001
74	Wu C, Xu Q, Cao Z, Pan D, Zhu Y, Wang S, Liu D, Song Z, Jiang W, Ruan Y, Huang Y, Qin N, Lu H, Qin H. The volatile and heterogeneous gut microbiota shifts of COVID-19 patients over the course of a probiotics-assisted therapy. Clin Transl Med. 2021 Dec;11(12):e643.	DOI: 10.1002/ctm2.643
75	Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, Yin H, Xiao Q, Tang Y, Qu X, Kuang L, Fang X, Mishra N, Lu J, Shan H, Jiang G, Huang X. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol. 2020 May;5(5):434-435.	DOI: 10.1016/S2468-1253(20)30083-2
76	Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology. 2020 May;158(6):1831-1833.e3.	DOI: 10.1053/j.gastro.2020.02.055
77	Yao Y, Cai X, Fei W, Ye Y, Zhao M, Zheng C. The role of short-chain fatty acids in immunity, inflammation and metabolism. Crit Rev Food Sci Nutr. 2022;62(1):1-12.	DOI: 10.1080/10408398.2020.1854675
78	Yeoh YK, Zuo T, Lui GC, Zhang F, Liu Q, Li AY, Chung AC, Cheung CP, Tso EY, Fung KS, Chan V, Ling L, Joynt G, Hui DS, Chow KM, Ng SSS, Li TC, Ng RW, Yip TC, Wong GL, Chan FK, Wong CK, Chan PK, Ng SC. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut. 2021 Apr;70(4):698-706.	DOI: 10.1136/gutjnl-2020-323020

ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)

79	Zhang F, Wan Y, Zuo T, Yeoh YK, Liu Q, Zhang L, Zhan H, Lu W, Xu W, Lui GCY, Li AYL, Cheung CP, Wong CK, Chan PKS, Chan FKL, Ng SC. Prolonged Impairment of Short-Chain Fatty Acid and L-Isoleucine Biosynthesis in Gut Microbiome in Patients With COVID-19. Gastroenterology. 2022 Feb;162(2):548-561.e4.	DOI: 10.1053/j.gastro.2021.10.013
80	Zhao Y, Liu Y, Li S, Peng Z, Liu X, Chen J, Zheng X. Role of lung and gut microbiota on lung cancer pathogenesis. J Cancer Res Clin Oncol. 2021 Aug;147(8):2177-2186.	doi: 10.1007/s00432-021-03644-0.
81	Zhou Y, Shi X, Fu W, Xiang F, He X, Yang B, Wang X, Ma WL. Gut Microbiota Dysbiosis Correlates with Abnormal Immune Response in Moderate COVID-19 Patients with Fever. J Inflamm Res. 2021 Jun 17;14:2619-2631.	doi: 10.2147/JIR.S311518.
82	Zhou B, Pang X, Wu J, Liu T, Wang B, Cao H. Gut microbiota in COVID-19: new insights from inside. Gut Microbes. 2023 Jan-Dec;15(1):2201157.	doi: 10.1080/19490976.2023.2201157.

ISSN 1563-0625 (Print)
ISSN 2313-741X (Online)