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COMMUNICATIONS BETWEEN PROTEINS AND GLYCOCONJUGATES IN ORGANISM INFECTED WITH COVID

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ABSTRACT

Antipathogen and antitumor potential of metabolite-cellular lectin supersystem of human organism including key contributor lectin systems such as postbiotics, probiotic proteins, complement, protein hormones and angiotensin-renin systems were evaluated. Postbiotics possess a broad extremely perspective potential against different groups of diseases. They are characterized as a coupled system within a network recognizing glycoconjugates. Postbiotics act according to functioning metabolic axes within mucosal open cavities among different type tissues and organs. Lectin supersystem serves the ancient basis for stabilization, prolongation and improvement of protective action of such effectors as meta/postbiotics, prebiotics and drugs of glycoconjugate origin. The action of protective lectin system involves cofunctioning to other systems of recognition and effector action (antibodies, cytokines, complement, antibiotics, drugs for chemotherapy). The action of the supersystem recognizing viral and other pathogens directly or indirectly is described on examples of diseases accompanied with *Covid*. On the basis of protein-glycoconjugate relationships and interactions, factors and ways of designing antiviral vaccines are indicated. Prospects of protective supersystem constituents are discussed. Expression and modulation of different lectin type recognition systems as supersystem in organism can be considered as a new way for development of new criteria for health of individual or contingents of individuals at the level of cell-metabolite communications.

KEYWORDS: postbiotics; Covid-19; SARS-CoV-1; SARS-CoV-2; diseases; lectin systems; glycoconjugates; complement; protein hormones; vaccines.

1. INTRODUCTION

Bio-recognition - the main initiating event in the functioning of human defense systems. The human body provides for the coordinated action of its own protective and microbial-symbiotic systems that recognize and bind pathogen-associated targets.[3,4,6] Examples of such metabolite-cellular defense systems can serve as innate immunity (complement and blood clotting systems, cytokine network, angiotensin-renin-blood pressure support system), and also symbiotic/ probiotic microbiocenoses. Protein hormones (cytokines with a broad spectrum of action) together with receptors form a glycoconjugate-recognizing (GC) defense system. Probiotic microorganisms exhibit evolutionarily developed properties useful for humans, producing a range of metabolic postbiotics. The latter include products of the life activity of symbiotic / probiotic microorganisms. They include not only low-molecular (antimicrobial peptides, including bacteriocins), but also high-molecular substances, compounds and their complexes such as adhesives and enzymes, biosurfactants (BS), exopolymer compounds (EPS), cell wall components (proteoglycans) and probiotic lectins (PL).[1,5,7] The biological properties of postbiotics are diverse and vary in sets of postbiotic systems (PS).[1,5,7,32-35]

Lectins include proteins, their (oligo) peptide derivatives of non-immunoglobulin nature, as well as complexes that recognize and bind carbohydrates and GC (natural or their synthetic polymer analogues, www.lectinity.com), initiating activities against infections and pathologies caused by them.[3,4] Lectins regulate the human metabolism, exhibit the properties of metabolomebiotics and are communicators. They are involved in a network of metabolites-cellular and intercellular relationships, strengthening the immune system.

The goal is to present modern ideas about protective postbiotic and other systems of non-immunoglobulin nature against diseases accompanied by *Covid* on the basis of our own results and literature data.

2. Therapeutically significant Postbiotics and PS[5,7,33,34]

An analysis of the literature indicates the usefulness and effectiveness of postbiotics (their combinations as PS coupled in a productive final action) against a wide range of different diseases initiated by pathogenic microorganisms and viruses or in connection with hereditary

and acquired metabolic disorders in the body. So, postbiotics make a health contribution in cases of enterocolitis, dysbiosis, food, allergies (interfering with normal vaccination), hepatitis, neurodegenerative diseases, hair loss, pathologies related to insulin and antibiotic resistance, disorders of fat and other metabolism.

PS of lactobacilli and bifidobacteria are the most studied. According to our data, antimicrobial action of *Acilact* can be implemented with the participation of PS – peroxide-reductase products under conditions of oxidative stress, caseinate products - at the level of action of the peptides and on the background of reducing allergenicity and PS involving sets BS (their generation depends on the strain). One of the *Acilact* strains (K_3III_{24}) is the dominant source of pronounced amounts of bacteriocin-like complex forms. Bifidobacteria, in addition to the production of BS (involved in the delivery of peptides), are characterized by varying images of PS, represented as strain-dependent sets of EPS (cleaved by endogenous depolymerases) with delayed antimicrobial action.

The action of postbiotics is realized in the metabolically directed axes [7, 32, 45, 58, 59] - with a generalized formula for the implementation of postbiotics "Biotopes of mucosal cavities of the intestinal tract - Other types of tissues and organs". The metabolic relationships of intestinal postbiotics with the liver, kidneys, lungs, brain, skin, and blood are established (it is possible to postulate the expansion of connections with other organs and tissues). PS are characterized as multi-functional and multi-vector, pleiotropic and multi-directional. They include immunomodulatory, anti-inflammatory, antitumor, anti-allergenic (the latter in cases of, for example, fermentolysis of polymer allergens with hydrolases), regulating the production of cytokines and other important types of effectors. The directed axial nature of the functioning of the metabolic network implies recognition of characteristic targets (including GC-containing ones) by postbiotics. The functioning of PS, including lectin type ones, is similar to the GC-dependent functioning of the PL and PL-GC networks (further recognition of GC types is modified in complexes with PL is possible) of the mucosal biotope.

3. The main areas of PS research

*Transition from empirically established multi-action of postbiotic fractions (probiotic culture fluid supernatants) to identification of the relative contribution of mono/bi/ multicomponent postbiotics and PS to the effector result.

*Construction of a new substation with the use of specific directional and predictable fermentation (selected types and combinations of isolated enzymes or enzymes in probiotic cultures).

*Development of technologies for using fractions of bacterial cell walls and their components as PS in combination with prebiotics.

*The use of PS in the prevention and accompanying treatment of diseases (systemic, primary and secondary, including autoimmune) and their combinations, including microbial and viral nature (including *Covid*).

*Expanding the consideration of groups of diseases and pathologies when using a single type of postbiotic or PS to detail and further standardize the multi-action of the drug.

*Unlimited expansion of taxonomic and strain composition as sources of potentially new synergistic PS against the background of solving the problem of minimizing and optimizing the required PS.

*Transplantation of intestinal microbiomes as sources of combined PS for accompanying therapy.[59]

*Study and application of eukaryotic PS (yeast origin, with the leadership of the available and industrially significant genus *Saccharomyces*), including those with antifungal potential.[7,37]

*Design and use of synergistic combinations of PS with phytobiotics, innate immunity factors (cytokines, cytokine-like proteins, complement, pattern-recognizing receptors (PRR), and metabolites).[7]

*Use of enzymebiotics (when considering communicative probiotic bifunctional enzymes with lectin and adhesive domains/(sorption modules) for polysaccharides and GC as postbiotics).[31]

*Use of postbiotics products of microbial Trp and Tyr metabolism (for example, the use of the Acilact (and its strains) and probiotic bifidobacteria cultures potential.[33,34]

*Use of PS against diseases involving eukaryotic pathogens such as *Candida* and *Protozoa* origin.[7,32,49]

*Study of the PS impact on viral diseases using examples of rotavirus (RV) diarrhea, viral hepatitis (C and related variants), viral pneumonia (RSV), and *Covid* pneumonia.[10,11,18,25,41,48,53,60]

*Use of PS against tumor cell cultures and to prevent the development of tumors *in vivo*.[7,9,42,47]

*Use of PS (synergistic and partially alternative) in connection with side effects of antibiotics.[7,43]

*Postbiotics against oxidative stress in tissues and organs (in the regulation of the enzymatic antioxidant system of the blood, intestines, and liver).[7]

* Development and application of PS in connection with children's diseases.[7,38,54]

*Development and application of PS in connection with food allergies.[7,40]

*Development of medical biotechnologies for designing PS:

- at the level of the controlled cell-wall fragmentation application;
- based on GC with a known structures;
- - based on micro/ nanoparticles and vesicle carriers of PS.

* Study of the PS effect on vaccines due to the PS multi-action[7,20,56] in aspects of:

- surface cell proteins of Gram-positive bacteria as components of PS and communication ingredients of vaccines;
- vaccines and immunomodulatory postbiotics;
- postbiotics in conditions of vaccine action (maintaining the natural normal level of metabolism);
- vaccines as GC, including those operating with the participation of the PS protection.

4. Prospects for the Study and Application of postbiotics

Glycosylation and production of GC are important factors in the development of vaccines and humanized glycoproteins.[8,20] Promising sources of synergistic sets of mucosal antimicrobial postbiotics involved in the GC recognition and binding serve human intestinal bifidobacteria and lactobacilli cultures. Individual postbiotics and PS that interact with GC exhibit the properties of lectins.

The linked network nature of the PS action indicates broad prospects for the PS using following aspects of studying and applying postbiotics in the future are of interest

*Search and investigation of new types and combinations of PS.

*Lectins as sources of postbiotics and PS with potential for therapy.[5,33]

*Development and application of PS in connection with solving fundamental problems of science:

- expanding functions of cellular immunity according to communication network of axial and other metabolic type defense systems common to the body;

- strengthening of biotopic infra - and signal functioning structures that are antagonistic to pathogens and pathogenesis factors, participation in the creation of highly resistant to pathogenic factors of age-related relationships of PS and body defense systems;
- multivalent compensation by the PS network for insufficient antibody protection;
- establishment (including empirically – for culture supernatant and its fractions) of promising PS compositions in connection with the tasks;
- study of the following PS action mechanisms:
-organ systems of open cavities: deeper detailed considered directions/ relationships between the intestine compartments; between intestines and urogenital tract, intestines and oropharynx;
-- in cases of disease initiated by a viruses;
-- in cases of diseases initiated by eukaryotic pathogens ([49], our data);
- typing of metabolic axes (typing of the network metabolomes with establishment of a set of co-functioning biochemical markers functionally linked within PS studied or tested);
- construction of functional food (search of key (co)factors), including composition of nutrient media or food additives, to enhance existing activities and/or regulate/switch activities in a given/wishable direction (against group of diseases, normalization of the type of metabolism, etc. [7]);
- ordering the action of postbiotics in the PS based on their interaction with GC in order to develop therapeutic/(therapeutically significant) and synergistic with antibiotics PS.[5,33,34]

5. The effects of protective non-immunoglobulin systems of the body against pathologies and diseases due to the presence of *Covid*

Covid viruses (SARS-CoV-1, SARS-CoV-2 and other groups of beta-1-*Covid*) cause *Covid*-19 diseases, are able to affect almost any (all) organs, show multi-functionality/ multi-action in target damage, act on vascular systems and cause rapid and, in some cases, significant amplification and adverse modification of existing chronic and systemic diseases. Therefore, it is particularly important to take into account the multi-functional multi-organ pathology-recognizing body defense systems that act as deep communications for superstructure anti-pathogenic attacks.[1,2,5]

5.1. The role of glycans in initiating and amplifying diseases in the presence of coronaviruses, including Covid variants. [8,12,14,17,20,23,24,29,41,55,58]

Marked high potential of the diversity of Lectin—Glycans/Glycosphingolipid interactions and their regulation in interprotein recognition processes involving carbohydrates as a co-receptor and co-determinant in the dissemination *Covid* in the body, as in cases of the SARCS CoV-2 lectin-like S-glycoproteins.[29]

Examples of the mutual recognition by natural GC - glycoproteins (envelope spike [Spike] trimer S-protein) of the *Covid* virus shell and receptor binding domain (RBD) of another glycoprotein - angiotensin-converting enzyme-2 - ACE-2 (Angiotensin-converting enzyme 2, EC 3.4.17.23) on alveolar epithelial cells to assess the contribution and role of GC (for example, non-protein configurations of glycans) and carbohydrates in the recognition and binding of *Covid*, including under interactions of lectins and GC. Upon contact with ACE-2 hydrolase, the protein S is cleaved into non-covalently bound S1 and S2 subunits, which are important for virus entry into the cell. Contact events are regulated by the density of the glycan layer and the variety of N-glycosidically bound (Asn-) and O-glycosidically bound (Ser/Thr-) glycans (including the ratio of complex and oligomannoside types of glycans) on the surface of both interacting glycoproteins (up to 40% of the protein surface).[8,14,17,24,41,58] Glycans affect the conformation of glycoproteins and form epitopes of corrective interaction in contacts. This is used in the design of vaccines against *Covid*.[17,23] The protein-S glycan shield serves as a therapeutic target for influencing the *Covid* molecular machine, for inactivating the virus, and for producing viral particles for use as vaccines.[17] In connection with the design of vaccines, it should be considered, for example, the effect of negatively charged diacetylated sialoglycans (Neu5,9Ac2-alpha-R) of the complex type in the protein S, as well as the enhancement of the effectiveness of the protein-S-based vaccine in the presence of an additional glycoengineering alpha-galactosyl epitope (Gal-alpha1-3Gal-beta1-4GlcNAc-R).[8,23]

As another way to combat *Covid*, it should be considered the construction of nanosurfaces loaded with antiviral polysaccharides (potential PS, including those with minimal chemical modifications) by "layer-on-layer"/ regulation of protein masking.[41] At the same time, in relation to the interaction of the *Covid* glycoprotein with a single binding site of ACE-2 in respect of penta-and longer-eiko-oligosaccharides of heparin (acidic sulfated glycosaminoglycan), they have the ability to prevent the interaction of *Covid* with human

cells against the background of maintaining a normal blood-clotting system (the system includes a lot of lectins such as ficolins and others).[19,50,55] The association of ACE 2 imbalance with dysbiosis (i.e., with a violation of the distribution and functioning of normal PS in mucosal biotopes) is considered as one of the key factors of low recovery in *Covid* patients of varying age.[51]

Another example of the involvement of intermolecular lectin-GC interactions in the spread of *Covid* infections is the involvement of the viral control "protein-virion-associated receptor – destroying lectin hemagglutinin esterase dimer" acting on multivalent GC in binding of the coronoviral protein S to the beta1-receptor of host cells.[12] As a result, the coronavirus adapts to the human/ patient respiratory tract glycome (the ability to switch protein-carbohydrate interactions).

When the SARS-CoV-2 protein S1 is expressed in the affected lung, the inhibitory receptor lectin NKG2A/CD94 is modulated on NK cells and the HLA-E/NKG2A pathway corresponding to the specific cascade intercellular reception of large-scale T-cell counteraction to viruses is activated using a variety of attacking specific cellular subpopulations of innate immunity.[4,13]

Individual functional features/differences in the recognition of human cells of very similar SARS-CoV-2 and SARS-CoV (serve vaccine candidates) were noted.[27] These include affinity for the cell receptor and the immunological ability of the virus to invade: a) RBD of the SARS-CoV-2 protein S is characterized by a greater affinity for the ACE2 receptor in comparison with SARS-CoV; b) RBD of the SARS-CoV-2 protein S can be located in one "up" and two "down" conformations, which indicates a predominant adaptation of the virus against the host's supracellular immune supervising.

5.2. Protective effects of complement system in relation to and against pathologies and diseases burdened by the presence of Covid.[16,21,26,28,31,39,57]

In *Covid* patients, systemic complement activation is registered, especially expressed within classical and lectin pathways, which leads to severe pulmonary insufficiency against the background of increased patient mortality.[26] Therefore, a general strategy to combat *Covid*-associated diseases is to target the whole or limited functioning of the complement system.

Consumption of C4 and/or C3 in the body with *Covid* infections leads to a decrease in normal levels of these complement components.[16,21,26] This is expressed in a decrease in the deposit of C4b (from C4) or C3b (from C3) fragments on the CR1 complement receptor lectin and the deposit of C4d (from C4) fragment in red blood cells of patients with *Covid*-19.[26,30] *Covid*-19 infections cause a greater decrease in blood flow levels of lectin-like components C4 and C3 (C4/C3) compared to SLE status. Both types of the disease lead to the development of antiphospholipid syndrome (AFS) and, as a consequence, thrombosis (therefore, it is possible to increase the syndrome in patients with SLE in the presence of *Covid* infection in the body).[16,38]

Patients with SARS-CoV-2 and SARS-CoV-1 are characterized with significantly increased activity of the lectin complement pathway.[26] reduced blood serum mannan-binding protein (MBP – another lectin of the complement system) through the viral activation of protease MASP-2 in complex with MBP, which initiates lectin complement pathway and generate C3-convertase (EC 3.4.21.43) by cleavage of C4 (additional consumption of C4/C3 in the body) and C2.[21,28,30] The coordinated action of complement with the blood clotting system was observed at the level of a variety of MBP and MASP variants (including the use of the same basic molecular forms of lectins and MASP-type ingredients that make up complex lectins),[50] which should increase the variety and effectiveness of anti-virus attacks. As a result, a supramolecular ensemble is formed that further lyses any cells opsonized with the virus. In addition to the lectin pathway, C4/C3 is consumed in the classical and alternative complement pathways, which ultimately (in all variants of these shunt pathways) lead to lysis of affected cells.

Thus, C4/C3 manifests itself as a “basis for superstructure” - key multifunctional system in demand in various shunt cascades of metabolic-cellular complement reactions, which can adapt to identified pathogen images by switching and reorienting protective responses (economization and universalization of responses is achieved using a minimum number of participants in lectin recognition in nodal cascades of divergence and convergence of the metabolomebiotic network).

Therapy strategies usually consist in limiting/ switching complement activation by partially disabling selective cascades of reactions in the complement metabolic-cellular network, including in connection with the linked functioning of the coagulation/ thrombosis system (the system taking into account the *Covid* action status). Therapeutically significant in cases

with Covid infections may be inhibition of the development of C3-related reactions and blocking of the C5 complement component, which prevents hyperinflammation and thromboinflammation in patients with *Covid*.[38] Options for limiting the effect of complement in patients due to *Covid* exposure to factors B and H (the latter is a typical (Sialic acids)–binding lectin with fine and superfine pattern specificity) are considered.[57]

5.3. Impact of EPO in relation to Covid infections.[22,36,44,45]

EPO, namely, a system of multiple forms that can interact with GC and exhibit a wide range of network interactomic biological activities, including through GC-sensitive cellular reception in many organs (lungs, liver, heart, brain, and others), is a candidate for accompanying/ supporting/counteracting/ adjuvant therapy of patients with *Covid* variants.[22,36,44,45] Since EPO functions as "more than an erythropoiesis hormone" (it participates in an extensive network of reactions with cellular receptors of other functional purposes, but involving the recognition and binding of GC), it is possible to implement tissue antiapoptotic effects, especially in organs affected by *Covid*-19.[36]

5.4. The protective role of PS in preventing the spread and amplification of Covid infections in the body.[10,11,25,41,46,60]

The relationship between dysbiosis in the body and the status of pathology (type of disease, its progression, age characteristics) in the presence of *Covid* infections is considered.[10,25,51,60] The directions of antiviral action of PS are emphasized in accordance with the metabolic axes "Gut—Lungs" and "Gut—Brain".[10,11,25,46] Thus, in the "Gut—Lung" direction, the microbiome is involved in cross-talk in cases of patients not only with *Covid*, but also (possibly against the background of) chronic obstructive pulmonary disease (COPD), cystic fibrosis, lung cancer, respiratory allergies, and asthma.[46]

Other metabolic axes of the anti-cancer effect of PS are also possible, since *Covid* infections are able to affect almost any organs and tissues. The prospects of PS in the direction of "Intestine—Prostate" remain open (men are more susceptible to diseases with *Covid*, diseases are accompanied by infertility, hair loss), which involves the participation of the transmembrane bifunctional protease "Serin-2" (TMPRSS2).[52]

Postbiotics have the potential to serve as biomarkers of metabolism adequate to the current status of *Covid* disease. Along with regulatory polysaccharides and EPS, acidic postbiotic microbial oligosaccharides and their derivatives seem to have the potential for anti-*Covid*

action, similar to animal-derived oligosaccharides, as in the case of heparin.[41] In general, there are prospects of PS in preventing the spread of coronaviral and other types of viral infections in the body, as well as combinations of infections burdened by the presence of *Covid*, in the development of therapeutic and preventive strategies and preparations against groups of diseases.

The ways of effective health-supporting effects of a non-immunoglobulin GC-recognizing super-system with postbiotic and probiotic responses to the presence of lectin-GC-relationships of *Covid* and other viral infections in the body discussed above open up reserves for the design of antiviral vaccines.[15,20,27]

6. CONCLUSIONS

The above data indicate that in the case of a PS

1. Postbiotics act as PS (cofunction within PS), which is expressed in countering groups of diseases (determining the composition of groups and directions of metabolic axes are under development). Acting in the direction of functionally linked metabolic axes, PS increase the safety of the body, increase the resistance of microbiocenoses of biotopes, tissues and organs to pathogenic and other environmental stress factors.
2. PL serve promising sources of therapeutically significant PS and other health-supporting types of PS. Highly molecular PS (mainly enzymes and their modulators, EPS and BS, polysaccharides and peptidoglycans) involved in the conversion rearrangement of PS compositions are promising.

The body's metabolic-cellular defense systems are coordinated hierarchically and synergistically in a single super-system of defense with probiotic and postbiotic effects. Antibody/ immunoglobulin systems act as superstructures based on basic non-antibody systems. On the example of *Covid* infections, pathologies and diseases, the protective potential of the healthy human/ patient metabolites-cellular super system is demonstrated.

REFERENCES

1. Lakhtin MV, Lakhtin VM, Melikhova AV, Davydkin IYu and Davydkin VYu. (2020). Non-Antibody Protective Systems of Organism against Diseases in the Presence of *Covid*. *Problems of Scientific Thought* (Dnepr, Ukraine) [*Problemy nauchnoy misli* (Dnepr, Ukraina)], 2020; 8(12): 16-31. ISSN 1561-6916. (in Russian). https://elibrary.ru/title_about.asp?id=56372.

2. Lakhtin VM, Lakhtin MV, Melikhova AV, Davydkin IYu and Davydkin VYu. (2020). Postbiotic and Other Metabolic Cell Systems of Health against *Covid* Infections and Diseases. *Problems of Scientific Thought* (Dnepr, Ukraine) [*Problemy nauchnoy misli* (Dnepr, Ukraina)], 2020; 6(10): 3-24. ISSN 1561-6916. (in Russian). https://www.elibrary.ru/item.asp?id=44069682.
3. Lakhtin MV, Lakhtin VM, Aleshkin VA and Afanasiev SS. (2019). NK-Cells that Identify Glycopatterns and Their Anti-Tumor Potential against a Background of Epidemically Significant Viral Infections. *Health Risk Analysis*, 2019; 1: 144-53. ISSN (Print) 2308-1155. ISSN (Online) 2308-1163. ISSN (Eng-online) 2542-2308. https://www.elibrary.ru/item.asp?id=37260852.
4. Lakhtin MV, Lakhtin VM, Afanasiev SS, Aleshkin VA and Mironov AYu. (2018). Lectins and Glycoconjugates in Antigen Presentation and Protection against Pathogens. *Russian Clinical Laboratory Diagnostics* (Moscow) [*Klinicheskaya Laboratornaya Diagnostika, (*Moskva)], 2018; 63(10): 619-25. DOI: http://dx.doi.org/10.18821/0869-2084-2018-63-10-619-625. ISSN: 0869-2084. (in Russian). https://elibrary.ru/contents.asp?titleid=7849.
5. Lakhtin MV, Lakhtin VM, Davydkin VYu, Melikhova AV, Davydkin IYu and Aleshkin VA. (2020). Postbiotics against Infections, Diseases and Other Pathologies. *Problems of Scientific Thought* (Dnepr, Ukraine) [*Problemy nauchnoy misli* (Dnepr, Ukraina)], 2020; 3(7): 3-21. ISSN 1561-6916. (in Russian). https://elibrary.ru/contents.asp?id=43179990.
6. Lakhtin MV, Lakhtin VM, Davydkin IYu, Melikhova AV and Davydkin VYu. (2020). Approaches to Study of Therapeutic Postbiotics. *Ural Scientific Bulletin* (Uralsk, Kazakhstan) [*Uralskiy nauchniy vestnik* (Uralsk, Kazahstan)], 2020; 3(5): 3-15. ISSN 1561-6908. (in Russian). https://elibrary.ru/item.asp?id=43112654.
7. Lakhtin MV, Lakhtin VM, Mironov AYu, Aleshkin VA and Afanasiev SS. (2020). The Human Lectin Supersystems with Probiotic and Postbiotic Actions. *Russian Clinical Laboratory Diagnostics* (Moscow) [*Klinicheskaya Laboratornaya Diagnostika, (*Moskva)], 2020; 65(4): 231-8. DOI: http://dx.doi.org/10.18821/0869-2020-65-4-231-238. ISSN: 0869-2084. (in Russian). https://elibrary.ru/item.asp?id=42596124.
8. Adamo R and Sonnino S. (2020). Impact of Glycoscience in Fighting Covid-19. *Glycoconjugate Journal*, 2020; 5: 1–2. DOI: 10.1007/s10719-020-09929-9.
9. Aguilar-Toalá JE, Hall FG, Urbizo-Reyes UC, Garcia HS, Vallejo-Cordoba B, González-Córdova AF [et al.]. (2019). In *Silico* Prediction and *In Vitro* Assessment of

Multifunctional Properties of Postbiotics Obtained From Two Probiotic Bacteria. *Probiotics and Antimicrobial Proteins*, 2019; 6. DOI: 10.1007/s12602-019-09568-z.

10. Aktas B and Aslim B. (2020). Gut-Lung Axis and Dysbiosis in *Covid*-19. *Turkish Journal of Biology*, 2020; 44(3): 265-72. DOI: 10.3906/biy-2005-102.
11. Andrade MC, de Faria RS and Nobre SAM. (2020). *Covid*-19: Can the Symptomatic SARS-CoV-2 Infection Affect the Homeostasis of the Gut-Brain-Microbiota Axis. *Medical Hypotheses*, 2020; 144: 110206. DOI: 10.1016/j.mehy.2020.110206.
12. Bakkers MJG, Lang Y, Feitsma LJ, Hulswit RJG, de Poot SAH, van Vliet ALW [et al.] (2017). Beta-coronavirus Adaptation to Humans Involved Progressive Loss of Hemagglutinin-Esterase Lectin Activity. *Cell Host and Microbe*, 2017; 21(3): 356-66. DOI: 10.1016/j.chom.2017.02.008.
13. Bortolotti D, Gentili V, Rizzo S, Rotola A and Rizzo R. (2020). SARS-CoV-2 Spike 1 Protein Controls Natural Killer Cell Activation via the HLA-E/NKG2A Pathway. *Cells*, 2020; 26, 9(9): 1975. DOI: 10.3390/cells9091975.
14. Bernardi A, Huang Y, Harris B, Xiong Y, Nand S, McDonald KA [et al.]. (2020). Development and Simulation of Fully Glycosylated Molecular Models of ACE2-Fc Fusion Proteins and Their Interaction with the SARS-CoV-2 Spike Protein Binding Domain. *PLoS One*, 2020; 5, 15(8): e0237295. DOI: 10.1371/journal.pone.0237295.
15. Bourgonje AR, Abdulle AE, Timens W, Hillebrands J-L, Navis GJ, Gordijn SJ [et al.]. (2020). Angiotensin-Converting Enzyme 2 (ACE2), SARS-CoV-2 and the Pathophysiology of Coronavirus Disease 2019 (COVID-19). *Journal of Pathology*, 2020; 251(3): 228-8. DOI: 10.1002/path.5471.
16. Cardoso EM, Hundal J, Feterman D and Magaldi J. (2020). Concomitant New Diagnosis of Systemic Lupus Erythematosus and Covid-19 with Possible Antiphospholipid Syndrome. Just a Coincidence? A Case Report and Review of Intertwining Pathophysiology. *Clinical Rheumatology*, 2020; 39(9): 2811-2815. DOI: 10.1007/s10067-020-05310-1.
17. Casalino L, Gaieb Z, Goldsmith JA, Hjorth CK, Dommer AC, Harbison AM [et al.], 2020. Beyond Shielding: The Roles of Glycans in SARS-CoV-2 Spike Protein // *bioRxiv preprint* DOI: https://doi.org/10.1101/2020.06.11.146522. The version posted September, 2020; 4.
18. Clua P, Kanmani P, Zelaya H, Tada A, Kober AKMH, Salva S [et al.]. (2017). Peptidoglycan from Immunobiotic *Lactobacillus rhamnosus* Improves Resistance of Infant Mice to Respiratory Syncytial Viral Infection and Secondary Pneumococcal

Pneumonia. *Frontiers in Immunology*., 2017; 10(8): 948. DOI: 10.3389/fimmu.2017.00948.

19. Cornish EF, Filipovic I, Åsenius A, Williams DJ and McDonnell T (2020). Innate Immune Responses to Acute Viral Infection During Pregnancy. *Frontiers in Immunology*, 2020; 30, 11: 572567. DOI:10.3389/fimmu.2020.572567.
20. Cuccui J and Wren B. (2015). Hijacking Bacterial Glycosylation for the Production of Glycoconjugates, from Vaccines to Humanised Glycoproteins. *The Journal of Pharmacy and Pharmacology*., 2015; 67(3): 338-350. DOI: 10.1111/jphp.12321.
21. Dheir H, Sipahi S, Yaylaci S, Köroğlu M, Erdem AF and Karabay O. (2020). Is there Relationship Between SARS-CoV 2 and the Complement C3 and C4? *Turkish Journal of Medical Sciences*, 2020; 18, 50(4): 687-688. DOI: 10.3906/sag-2004-336.
22. Ehrenreich H, Weissenborn K, Begemann M, Busch M, Vieta E and Miskowiak KW. (2020). Erythropoietin as Candidate for Supportive Treatment of Severe *Covid-19*. *Molecular Medicine*, 2020; 26: 58. DOI: 10.1186/s10020-020-00186-y.
23. Galili U. (2020). Amplifying Immunogenicity of Prospective *Covid-19* Vaccines by Glycoengineering the Coronavirus Glycan-Shield to Present alpha-Gal Epitopes. *Vaccine*, 2020; 38: 6487–6499.
24. Grant OC, Montgomery D, Ito K and Woods RJ (2020). Analysis of the SARS-CoV-2 Spike Protein Glycan Shield Reveals Implications for Immune Recognition. *Scientific Reports*, 2020; 10: 14991. DOI: https://doi.org/10.1038/s41598-020-71748-7.
25. He L-H, Ren L-F, Li J-F, Wu Y-N, Li X and Zhang L. (2020). Intestinal Flora as a Potential Strategy to Fight SARS-CoV-2 Infection. *Frontiers in Microbiology*, 2020; 9(11): 1388. DOI: 10.3389/fmicb.2020.01388.
26. Holter JC, Pischke SE, de Boer E, Lind A, Jenum S, Holten AR [et al.]. (2020). Systemic Complement Activation is Associated with Respiratory Failure in COVID-19 Hospitalized Patients. *Proceedings of National Academy of Sciences of U S A*, 2020; 6, 117(40): 25018-25. DOI: 10.1073/pnas.2010540117.
27. Izda V, Jeffries MA and Sawalha AH. (2020). COVID-19: A Review of Therapeutic Strategies and Vaccine Candidates. *Clinical Immunology*, 2020; 17: 108634. DOI:10.1016/j.clim.2020.108634.
28. Java A, Apicelli AJ, Liszewski MK, Coler-Reilly A, Atkinson JP, Kim AH [et al.]. (2020). The Complement System in *Covid-19*: Friend and Foe? *JCI Inight*, 2020; 6, 5(15): e140711. DOI: 10.1172/jci.insight.140711.

29. Kim C-H. (2020). SARS-CoV-2 Evolutionary Adaptation toward Host Entry and Recognition of Receptor O-Acetyl Sialylation in Virus-Host Interaction. *International Journal of Molecular Sciences*, 2020; 26, 21(12): 4549. DOI:10.3390/ijms21124549.
30. Kisserli A, Schneider N, Audonnet S, Tabary T, Goury A, Cousson J [et al.], Acquired Decrease of the C3b /C4b Receptor (CR1, CD35) and C4d Deposits on Erythrocytes from ICU COVID-19 Patients // *medRxiv preprint*, 2020. DOI: https://doi.org/10.1101/2020.08.10.20162412.
31. Lakhtin MV, Lakhtin VM and Alyoshkin VA (2020). Lectin and Enzyme Relationships in Microbiology. *International Journal of Molecular and Clinical Microbiology* (IJMCM), 2011; 1(1): 9-14. ISSN: 2008-9171.
32. Lakhtin VM, Lakhtin MV and Davydkin VYu. (2020). Bifidobacteria – Sources of Antimycotic Systems. Proceedings of the International Conference "Process Management and Scientific Developments" (Peking, China, August 5, 2020). Scientific publishing house Infinity, 2020; 1: 120-128. ISBN 978-5-905695-64-3. DOI: https://doi.org/10.34660/INF.2020.27.65.002.
33. Lakhtin VM, Lakhtin MV, Davydkin VYu, Melikhova AV and Davydkin IYu. (2020). Pathways from Probiotic Lectins to Therapeutic Postbiotics. *Problems of Scientific Thought* (Dnepr, Ukraine) [*Problemy nauchnoy misli* (Dnepr, Ukraina)], 2020; 3(6): 3-14. ISSN 1561-6916. https://elibrary.ru/contents.asp?id=43136003.
34. Lakhtin VM, Lakhtin MV, Davydkin VYu, Melikhova AV, Davydkin IYu and Aleshkin VA (2020). Relationships Between Probiotic Lectins and Postbiotics. *World Journal Advanced Research Review* (WJARR), 2020; 7(1): 142-8. DOI: 10.30574/wjarr.2020.7.1.0234. e-ISSN 2581-9615.
35. Lakhtin VM, Lakhtin MV, Davydkin VYu, Melikhova AV and Davydkin IYu and Zhilenkova OG. (2020). Postbiotic and Other Protective Molecules Recognizing and Binding Glycoconjugates in Mucosal Organs. *American Scientific Journal*, 2020; 43(1): 4-12.
36. Leventhal J, Angeletti A and Cravedi P. (2020). EPO in Patients With COVID-19: More Than an Erythropoietic Hormone. *The American Journal of Kidney Diseases* (AJKD), 2020; 76(3): 441. DOI: 10.1053/j.ajkd.2020.06.002.
37. Lohith K, Anu-Appaiah KA and Reeta PR. (2020). Application of Probiotic Yeasts on *Candida* Species Associated Infection. *Journal of Fungi*, 2020; 6: 189. DOI: 10.3390/jof6040189

38. Malagón-Rojas JN, Mantziari A, Salminen S and Szajewska H. Postbiotics for Preventing and Treating Common Infectious Diseases in Children: A Systematic Review. *Nutrients*, 2020; 12(2): 389. DOI: 10.3390/nu12020389.
39. Mastellos DC, da Silva BGPP, Fonseca BAL, Fonseca NP, Auxiliadora-MartinsM, Mastaglio S [et al.]. (2020). Complement C3 vs C5 Inhibition in Severe *Covid-19*: Early Clinical Findings Reveal Differential Biological Efficacy. *Clinical Immunology*, 2020; 220: 108598. DOI: 10.1016/j.clim.2020.108598.
40. Nataraj BH, Ali SA, Behare PV and Yadav H. (2020). Postbiotics-parabiotics: The New Horizons in Microbial Biotherapy and Functional Foods. *Microbial Cell Factors*, 2020; 20, 19(1): 168. DOI: 10.1186/s12934-020-01426-w.
41. Otto DP and de Villiers MM. (2020). Layer-by-Layer Nanocoating of Antiviral Polysaccharides on Surfaces to Prevent *Coronavirus* Infections. *Molecules*, 2020; 25(15): 3415. DOI: 10.3390/molecules25153415
42. Panebianco C, Andriulli A and Pazienza V. (2018). Pharmacomicrobiomics: Exploiting the Drug-Microbiota Interactions in Anticancer Therapies. *Microbiome.*, 2018; 22, 6(1): 92. DOI:10.1186/s40168-018-0483-7.
43. Puccetti M, Xiroudaki S, Ricci M and Giovagnoli S. (2020). Postbiotic-Enabled Targeting of the Host-Microbiota-Pathogen Interface: Hints of Antibiotic Decline? *Pharmaceutics*, 2020; 12(7): 624. DOI: 10.3390/pharmaceutics12070624.
44. Sahebnasagh A, Mojtahedzadeh M, Najmeddin F, Najafi A, Safdari M, Ghaleno HR [et al.]. (2020). A Perspective on Erythropoietin as a Potential Adjuvant Therapy for Acute Lung Injury/Acute Respiratory Distress Syndrome in Patients with *Covid-19*. *Archives of Medical Research*, 2020; 11. DOI: 10.1016/j.arcmed.2020.08.002.
45. Soliz J, Schneider-Gasser EM, Arias-Reyes C, Aliaga-Raduan F, Poma-Machicao L, Zubieta-Calleja G [et al.]. (2020). Coping with Hypoxemia: Could Erythropoietin be an Adjuvant Treatment of *Covid*-19? *Respiratory Physiology & Neurobiology*, 2020; 279: 103476. DOI: 10.1016/j.resp.2020.103476.
46. Srinath BS, Shastry RP and Kumar SB. (2020). Role of Gut-Lung Microbiome Crosstalk in COVID-19. *Reseach on Biomedical Engineering*, 2020; 24; 1–11. DOI:10.1007/s42600-020-00113-4.
47. Rad AH, Aghebati-Maleki L, afil HS and Abbasi A. (2020). Molecular Mechanisms of Postbiotics in Colorectal Cancer Prevention and Treatment. *Critical Reviews in Food Science and Nutrition*, 2020; 15: 1-17. DOI:10.1080/10408398.2020.1765310.

48. del Rigo-Adrover MM, Knipping K, Garssen J, van Limpt K, Knol J, Franch A [et al.]. (2019). Prevention of *Rotavirus* Diarrhea in Suckling Rats by a Specific Fermented Milk Concentrate with Prebiotic Mixture. *Nutrients*, 2019; 11(1): 189. DOI: 10.3390/nu11010189.
49. Rossoni RD, de Barros PP, Mendonça IDC, Medina RP, Silva DHS, Fuchs BB [et al.]. (2020). The Postbiotic Activity of *Lactobacillus paracasei* 28.4 Against *Candida auris*. *Frontiers in Cell Infection and Microbiology*, 2020; 4, 10: 397. DOI: 10.3389/fcimb.2020.00397.
50. Świerzko AS and Cedzyński M. (2020). The Influence of the Lectin Pathway of Complement Activation on Infections of the Respiratory System. *Frontiers in Immunology*, 2020; 21, 11: 585243. DOI: 10.3389/fimmu.2020.585243.e.
51. Viana SD, Nunes S and Reis F. (2020). ACE2 Imbalance as a Key Player for the Poor Outcomes in COVID-19 Patients with Age-Related Comorbidities – Role of Gut Microbiota Dysbiosis. *Ageing Research Reviews*, 2020; 62: 101123. DOI:10.1016/j.arr.2020.101123.
52. Wambier CG, Goren A, Vaño-Galván S, Ramos PM, Ossimetha A, Nau G [et al.]. (2020). Androgen Sensitivity Gateway to COVID-19 Disease Severity. *Drug Development Research*, 2020; 81(7): 771-6. DOI: 10.1002/ddr.21688.
53. Wang Y, Pan CQ and Xing H. (2019). Advances in Gut Microbiota of Viral Hepatitis Cirrhosis. *BioMed Research International.*, 2019; 22, 2019: 9726786. DOI: 10.1155/2019/9726786.
54. Wegh CAM, Geerlings SY, Knol J, Roeselers G and Belzer C. (2019). Postbiotics and Their Potential Applications in Early Life Nutrition and Beyond. *International Journal of Molecular Science*, 2019; 20(19): 4673. DOI: 10.3390/ijms20194673.
55. Yang Y, Du Y and Kaltashov IA. (2020). The Utility of Native MS for Understanding the Mechanism of Action of Repurposed Therapeutics in *Covid-19*: Heparin as a Disruptor of the SARS-CoV-2 Interaction with Its Host Cell Receptor. *Analytical Chemistry*, 2020; 18, 92(16): 10930-10934. DOI: 10.1021/acs.analchem.0c02449.
56. Yao Ang Y, Sano M, Dan S, Leelakriangsak M and Lal TM. (2020). Postbiotics Applications as Infectious Disease Control Agent in Aquaculture., 2020; 25(1): 1-7. DOI: 10.4265/bio.25.1.
57. Yu J, Yuan X, Chen H, Chaturvedi S, Braunstein EM and Brodsky RA. (2020). Direct Activation of the Alternative Complement Pathway by SARS-CoV-2 Spike Proteins is

Blocked by Factor D Inhibition. *Blood*, 2020; 29, 136(18): 2080-9. DOI: 10.1182/blood.2020008248.

58. Zhao P, Praissman JL, Grant OC, Cai Y, Xiao T, Rosenbalm KE [et al.]. (2020). Virus-Receptor Interactions of Glycosylated SARS-CoV-2 Spike and Human ACE2 Receptor *Cell Host & Microbe*, 2020; 24, S1931-3128(20)30457-1. DOI: 10.1016/j.chom.2020.08.004.
59. Zheng D, Liwinski T and Elinav E. (2020). Interaction Between Microbiota and Immunity in Health and Disease. *Cell Research*, 2020; 30(6): 492–506. DOI: 10.1038/s41422-020-0332-7.
60. Żółkiewicz J, Marzec A, Ruszczyński M and Feleszko W. (2020). Postbiotics—A Step Beyond Pre- and Probiotics. *Nutrients*, 2020; 12(8): 2189. DOI: 10.3390/nu12082189.