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Chapter

Metabolite Multiprobiotic Formulas for Microbial Health

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Abstract

On example of *Lactobacillus* and *Bifidobacterium* strains, approaches in creation of human multistrain probiotic metabolite mixtures for different goals were proposed. Human probiotic lectin systems (LS) (mucosal, others) reveal functions needed for organism. Advanced features of such systems include capability to recognize synthetic polymeric polyvalent glycoconjugates (GC)—imitators of natural ones (modified polysaccharides, glycoantigens of medical significance). Probiotic lectin systems function as imitators of multipro-/sym-/synbiotics in their resulting actions. They serve as carriers of the biotope glycoconjugate décor including glycoprebiotics, glycometabiotics, glycodrugs, and agents supporting décor organization and resistance. Probiotic lectin systems represent new perspective system agents to improve the health of mucosal microbiocenoses (MB) organized as communicative bodies to be corrected according to the principle "there is body—there are diseases." They act as metabolomebiotics according to the principle "the network in the network." They deepen biotope resistance allowing quicker return to balance. They support prophylactic and therapeutic procedures directed to prolong aging and improve quality of life. Multistrain metabolite constructions can predict perspective cellular formulas of multipro-/synbiotics for prophylaxis, supporting and accompanying therapy. Approaches developed are universal. They are useful in the study of any Gram-positive and eukaryotic (yeasts and yeast-like fungi) mono- and mixed cultures. The methodological principles proposed and described are of value for extended fields of clinical microbiology and medical bio-/nanotechnology.

Keywords: multistrain probiotics, probiotic lectins, glycoconjugates, microbiocenoses, antimicrobials

1. Introduction

Pro-/sym-/synbiotics are important objects of human microecology and medical biotechnology [1–4]. Microbes and human communicate each other by the way of recognition and binding glycoconjugates (GC) of varying pattern complexity by proteins (mainly adhesions and lectins) [5–9]. Lectin systems (LS) of symbiotic/probiotic microorganisms (LSSM) recognizing GC represent new multifunctional factors [8–12]. LSSM are relatedly useful for human protein-/peptide-containing compounds and their complexes recognizing GC. LSSM reveal features of imitators of probiotics; members of new class of bacteriocin-like destructors of biofilms of yeast-like fungal and Gram-positive pathogens; systems cofunctioning together

with enzymes of all known classes; and agents possessing antipathogenic synergism of different LS in antimicrobial combinations (between LS of *Lactobacillus* species and *Bifidobacterium* species, between genera *Lactobacillus* and *Bifidobacterium*, between LS of probiotic bacteria and lectins from medical plants, between LSSM and antibiotics) (see **Table 2**) [8, 9, 13, 14].

LS reveal significantly higher multifunctionality (antimicrobial, cytokine-like, others) and adaptive ability in surroundings in comparison to any component of LS. Applied prospects of LSSM in microbial associations of biotopes in the human body are of promised interest. LSSM and their reactive GC support balanced functioning in organism in respect to evolutionary created mucosal organ-like infrastructures of mutual interest for human and biotope microbiocenoses (MB) [12].

The purpose of the review is to evaluate our approaches in creation of probiotic metabolite compositions influencing and improving health of human biotope microbiocenoses. The data presented will be of interest for investigators in the fields of both medical microbiology and laboratory and industrial medical biotechnology.

2. Methods

Lactobacillus and *Bifidobacterium* strains were from the collection of microorganisms of the normal microflora of *G. N. Gabrichevsky* Institute for Epidemiology and Microbiology, and probiotics *Bifidin* and *Acilact* were products of our institute. Bacteria were grown in media containing casein hydrolysate and yeast autolysate. LSSM were extracted from the protein fractions 27–220 kD using isoelectrofocusing (IEF) in a plate of polyacrylamide gel (PAG) in a gradient of pH 4–8. Identification of proteins was performed by electroblotting on a hydrophobic membrane and staining with SYPRO blot stain (Bio-Rad Lab.). Nonstained proteins were evaluated by other spectrophotometric methods. The distribution of LSSM among proteins was determined by treatment of blots with biotinylated GC (GC-b) containing multiple residues of sugar(s) linked to the polyacrylamide (PA) linear core (like in external phenotypes of mucins and mucin-type glycans) (www.lectinity.com;

1.	α/β-D-GalNAc-PA-b (animal mucins, T antigens)*
2.	β-D-GalNAc-PA-b (animal mucins)
3.	β-D-GlcNAc-PA-b (insect chitins and chitosans)
4.	β-D-Gal-PA-b (plant or animal galactans)
5.	β-D-Gal-3-sulfate-PA-b (acidic animal galactans)
6.	α-D-Man-PA-b (yeast mannans)
7.	α-D-Man-6P-PA-b (yeast phosphomannans)
8.	α-L-Fuc-PA-b (fucans from brown algae)
9.	α-L-Rha-PA-b (Gram-negative rhamnans)
10.	MDP-PA-b (bacterial peptodoglycans)
11.	Adi-PA-b (A-blood group substance GalNAcβ1-3GalβA1-)
12.	Fs-PA-b (Forssman antigen GalNAcβ1-3GalNAcβA1-)
13.	Tαα-PA-b (bacterial antigen Galα1-3GalNAcα1-)

**In brackets—natural substances which are imitated*

Table 1.
A list of synthetic GC used.

Table 1) followed by final treatment with streptavidin-peroxidase conjugate. The bound peroxidase on the blot was registered in the presence of a chemiluminescent substrate in regime of a real time in the system BioChemi System (UVP, CA). Antimicrobial activities and synergism of LSSM, antibiotics, and phytolectins were tested on solid agar media during the prolonged growth and survival of communicative fungal bodies (CFB) in the presence of disks of antimicrobials. Biosurfactants were tested and calculated using detection of sample drop activity against mineral oil film on water surface (the appearance of transparent circles). Amino acid compositions of samples were established using standard amino acid analyzer column chromatography. Oxidoreductase systems were detected on blots after IEF-PAG, resulting in kinetic protein stain disappearance (decolorization). Hydrolase systems were visually evaluated on blots after IEF-PAG (resulting in hydrolysis, splitting, and partial asymmetrical disappearance of protein bands). *Maillard* reaction products were partially evaluated as browning in culture supernatant according to optical density at 420 nm.

3. Results and discussion

3.1 Symbiotic lectins as system regulators and delivery agents

LSSM function as metabolomebiotics regulating metabolome according to the principle "LSSM network—whole organism metabolome network or interactome" [15]. The network of LSSM is created in the following manner: lectin molecule of determined molecular weight (in the *Laemmli* system) is represented by LS including forms of varying charge and possessing a range of biological and physiological activities; such a minimal LS can be further transformed in a natural manner into extended network of complexes and supramolecular ensembles as a result of directional and sequential cascade binding of carbohydrates and GC. As a result of forming complexes and ensembles, lectin specificity of complexes and ensembles can be modified or changed during further development of recognition cascade network that will change the summary vector of specificity of LS. The latter will result in dynamic qualitative and quantitative changes of the local biotope surrounding. Thus, the final whole resulting network of LSSM (as metabolomebiotics) will regulate the whole metabolome and interactome of organism involving human glycome (carbohydrates and GC: glycoproteins, glycoenzymes, glycolipids, receptors, and others [16]). The metabolome possesses the ability to back direct and reversible effects of LSSM representing a part of hierarchic interactome. Multiple forms of adapted functioning LSSM microbiocenosis in the biotope will depend on the originality developed in a joint process of evolution involving host body local infrastructures for the distribution and disposition of microbiocenoses (organ-type constructions of both host and microbiocenosis interests are possible) [11, 12]. LSSM are ready to realize biologically active GC (as prebiotics, therapeutic agents, and metabiotics) in such symbiotic organs. The network of LSSM functions as noncellular simulators of symbiotics (probiotics) in the direct or indirect (through human higher hierarchic protection systems) predictable manners. For example, of communications between LSSM and own human protection systems, LSSM (as well as phytohemagglutinins from plants of medical significance) and artificial polymeric GC influenced peritoneal macrophage mobility in a coupled manner depending on doses of agents; LSSM were involved in modulation of cytokine production by human blood leukocytes [9, 17].

New useful properties of LSSM can be predicted and verified (cofunctioning to enzymes, adhesion, etc.), based on the fact that LSSM form a functional

superfamily of symbiotic lectins (on example of probiotic lectins and lectins of nitrogen-fixing bacteria). In addition, LSSM are members of the new class of destructors of biofilms of yeast-like and Gram-positive pathogens that simplify antimicrobial choice of components among LSSM. Other possibilities to operate with LSSM include their potential participation in a set of hierarchic pathways of advanced human innate protective systems in biotopes for *cross talks*. Both types of communications allow LSSM to be a successful synergistic assistant against pathogens in biotopes together with other antimicrobials and antimicrobial physical stress factors. As a result, LSSM reveal prolonged (early and late) anti-*Candida* activities as cascade (coupled) actions possibly influencing microecological niches of pathogens within biotope [registered during coculturing in the first 3 days (early events; also involving probiotic-like leader strains of *L. acidophilus* and *L. casei*), 1–2 weeks, or 2–3 months (late events)] [18].

The used GC are characterized with known chemical structures simplifying interpretation and prognostics of results. Such GC reveal potential of metabiotics which may use LSSM as carriers [8, 12, 19]. As highly homogenous, synthetic GC better functionally imitate natural GC targets [bacterial proteoglycans, fungal (phosphor)mannans, others] important for antimicrobial/anti-infectious actions of LSSM. As a result, LSSM are very perspective in delivery and deposition of adequate specific GC which are locally releasing as therapeutics possessing anti-infectious, prebiotic, and/or communicative signal abilities and actions.

In biotopes LSSM participate in continuous (on-duty) support and periodical (biorhythmic) completion and exchange of normal GC décor of cells, tissues, and organs that must provide delaying or stopping further the development of the spot/island/mosaic-landscape-originated and directed/metastasized abnormal processes as well as conserve any negative currently developmental events (initiation of appearance and survival of tumor-like cells as a result of innate intercellular communications involving lectin receptor-coupled cell surface receptor mosaics).

LSSM (natural combinative sets of LSSM-GC complexes) influence all yeast-like fungal phases of life by prolonging the degradation and lysis of pathogenic microbiocenosis massifs or biofilms in human biotopes (on examples of *Candida* species). In respect to CFB functioning as niches, lectins of lactobacilli (LL as preferentially mucins/mucus-recognizing) and lectins of bifidobacteria (BL as preferentially mannan-recognizing) synergistically act against internal and peripheral subniche territories, respectively. The late destructive and lytic events in CFB may also take place due to LSSM cooperative complex action as metabolomebiotics together with hydrolases involved in pathogen destruction network. Synergistic actions between LSSM and other antifungals increase resulting in final (early or late [also of apoptotic origin]) antipathogenic events as shown in **Table 2** [20].

Endogenous LS antimicrobial actions (e.g., intestinal probiotic bifidobacterial and lactobacillar LS against intestinal yeast-like fungi) provide more directed, sensitive, and completed resulting effectiveness against pathogens (the primary absence and further late complete destruction of residual resistant colonies in external and internal regions of CFB of *Candida albicans*) compared to the action of phytolectin mixture from grasses of medical significance in the same conditions. In cases of antibiotic-resistant strains, relatively sensitive to LSSM *C. albicans* strain 547 (less potentially pathogenic compared to the strain 515, see below), the sorbed lactobacillar cationic LS revealed their synergistic ability to "regenerate" original anti-*Candida* effectiveness of antibiotic (on example of nystatin) in the internal region of CFB of yeast-like fungus (appearance of pathogen-free landscape connected to the border of the disk antibiotic). The phenomenon of synergistic reparation of the original ability of the sorbed antibiotic indicates prospects of additional mechanisms of LSSM combinative actions and partially

describes how to increase resulting antifungal effectiveness during prolonged contact to pathogenic CFB at fungal late steps. In the case of more resistant (potentially "more pathogenic") fungal strains (like *C. albicans* strain 515), the sorbed

Types of synergism	**Lectins***	**Distant positions (directions from left to right)**	**CBF as targets, affinity, and significance**
Between PL			
Between identical PL disks	aBL and aBL	p-aBL, c-aBL (p-aBL—c-aBL)	*C. albicans* 991
Intra-genus (*Lactobacillus*)	cLL and aLL aLL and cLL	From p-cLL to CR (p-cLL—p-aLL) From p-aLL to CR (p-aLL—p-cLL)	*C. albicans* 515, 547 *C. albicans* 515, 547
Intra-genus (*Bifidobacterium*)	aLL and aBL	p-aLL and c-aBL (p-aLL—c-aBL)	*C. albicans* strains
Intra-genus (*Bifidobacterium*)	aBL and cBL	[PR aBL] and [CR aLL]	*C. albicans* strains
Inter-genera (*Lactobacillus* and *Bifidobacterium*)	aBL and aLL aLL and aBL	[PR aBL] and [CR aLL] (p-aBL—p-aLL) [PR aLL] and [CR aBL]$_2$* (p-aLL—p-aBL)	*C. albicans* strains *S. aureus* strains
Between PL and phytolectins			
Between PL and grass lectins (GL)	aLL and GL cBL and GL	From aLL to CR (p-MGBL—p-aLL) From p-cBL to CR (p-MGBL—p-cBL)	*C. albicans* 515 *C. albicans* 515
Between PL and antimycotics			
Between PL and amphotericin B	aBL	p-Amphotericin B, c-aBL (p-Amphotericin B—c-aBL)	*C. albicans* strains > *C. tropicalis* strains
Between PL and itraconazole	aBL	c-Itraconazole, p-aBL (p-Itraconazole—p-aBL)	*C. albicans* strains
Between PL and ketoconazole	aBL	p-Ketoconazole, c-aBL (p-Ketoconazole—c-aBL)	*C. albicans* strains
Between PL and nystatin	cLL cBL	From p-cLL to CR (p-cLL—c-nystatin) From cBL to CR (p-cBL—c-Nystatin)	*C. albicans* 515, 547 *C. albicans* 515, 547
Between GL and nystatin	GL	From p-MGBL to CR (p-MGBL—c-nystatin)	*C. albicans* 515
Multiple synergism			
Between BL and LL	aBL, aLL	In triangle of CFB landscape: p-aBL + c-aBL + p-aLL (p-aBL—c-aBL; p-aLL—c-aBL)	*C. albicans* strains (Not for *C. tropicalis*)

**Diffusion between disks placed on Sabouraud agar in Petri dishes (disk positions: p, peripheral; c, central; CR, central region, between p-disk and the center; PR, peripheral region, between p-disk and the border of agar). Disks included anionic (a) and cationic and (c) lactobacillar and bifidobacterial LSSM (aLL, cLL, aBL, cBL). MGBL as the mixture of the grass lectins from the mill of plants of medical significance: Potentilla album and Stellaria media. Lectins were used in subhemagglutinating doses (less 1 microgram/ml). Standard panel of disk antimycotics (HiMedia Lab. Pvt. Ltd.) was used. CFB, communicative fungal bodies.*

Table 2.
Antimicrobial synergism of LSSM and antibiotics.

bifidobacterial cationic LS synergistically increased anti-*Candida* action of the grass phytolectin mixture.

Results indicate that LSSM may also participate in temporary separation and conservation of natural infectious biofilms to prevent early visual landscape development of diseases. The latter may be perspective as the assistant factor of improving quality of life (its prolongation, mucus and skin reparations, cosmetic significance, etc.) as it can be expected using symbiotics [21].

On the whole, our experimental approach (observations of antagonistic relationships between LSSM and pathogens in prolonged stress conditions) and the data obtained are supported by the conception describing microecological stress events in organism as the normal but sensor natural reactions [22].

3.2 The choice of strains and their consortia possessing potential for constructing new multistrain pro- and symbiotics

Screening, choice, and selection of new or improved antimicrobial and other useful properties of symbiotic (probiotic) cultural properties of strains and consortia of human MB are important and strategic goals in prophylaxis and therapy of diseases, increasing resistance of organism and the acceleration of patient rehabilitation [1–4, 23]. Among GC investigated, glycans of mucin type (mucosal glycans) reveal special interest [24].

On the basis of own results, we proposed new algorithm of screening adequate probiotic-like microorganisms and their consortia possessing increased directed anti-infectious LS to construct new multipro-/sym-/synbiotics. The algorithm using LSSM (involving complexes to GC) among a panel of key factors in creating multiprobiotics (MP) included (a) the choice of synthetic GC-imitating bacterial proteoglycans and (phospho)mannans of yeast-like fungi; (b) identification of different LSSM (GC-type-dependent) among proteins of cultural fluids of probiotic strain or consortium of strains; (c) comparison of (GC-type)-dependent LS (evaluation of summary LS intensity, length of LS distribution in pH-gradient tested, mosaic asymmetric configuration of distributed forms in LS, major forms as dominating in contribution to antimicrobial actions of LS, minor forms as expressing signal regulators of biorecognition in microbiocenoses, signals of communications to surrounding infrastructures, as well as additional participants of recognition of new types of biomarker GC); (d) identification of unique sets of components of LS significant for typing strains, species, or genera; (e) revealing and choice of combinative sets of potential antimicrobial forms of LS for further control and testing; and (f) control of antimicrobial activities initiated, supported, and/or influenced by LS-containing preparations in other (nondependent) methods.

The data which were useful for constructing any multiprobiotics (*Acilact*-like) is presented in **Table 3**.

In **Table 3** the data needed for constructing formulas of any MP are presented on example of strain component compositions of *Acilact* (the well-known MP which served as a model). Algorithm for constructing formulas includes a few steps:

The first step: For formulas of any MP of category A (formulas as sum of wishful selected superiorities): the choice of all parameters of superiorities of MP (No. 4 as MP in code notes: positions 1.3, 1.4, 1.6, 2.7, 2.8, 2.13, 2.14, 2.15, and 4.3; major ingredient strain contributors are at the second position in the code sequences [from left to right] position in code).

The second step: For formulas of any MP of category B: accounting additional superiorities of MP [No. 4 as MP in code notes; selected minimal positions of parameters for No. 4 in sequence indicate maximal expression of the contrary (by implicity) parameters]. For example, in the case of No. 4 in codes 1.1

No.	Parameters of supernatants, ranging MP and its strains, proposals (P)	Code ranging MP and its strains*
1	Status of proteins	
1.0	Content of partially hydrolyzed protein K3III24 > MP > 100 ash > NK1 P: K3III24 as the main source of active or signal oligopeptides	3. 4. 2. 1.
1.1	Acidic proteins pI 4–5 NK1 > 100 ash > K3III24 > MP P: NK1 as the main source of basis cytoagglutinating and adhesive agents coupled to a spectrum of biological activities	1. 2. 3. 4.
1.2	Cationic proteins pI 7–8 NK1 > K3III24 > 100 ash > MP P: Strains and their combinations as sources of lectins and lectin-like agents coupled to exopolymeric substances of compounds	1. 3. 2. 4.
1.3	Oxidase-reductase systems pI 5–5.5 MP > 100 ash > K3III24 > NK1[absence] P: NK1 without extracellular major oxidoreductase systems	4. 2. 3. 1.
1.4	Hydrolase systems MP > K3III24 > 100 ash > NK1 P: NK1 without extracellular major hydrolases (caseinases, peptidases, others)	4. 3. 2. 1.
1.5	Level of aggregation upon storing concentrates K3III24 > 100 ash > NK1 > MP[no aggregation] P: Irreversibility for K3III24 (similar to red cell biofilm storing)	3. 2. 1. 4.
1.6	Ability in membrane ultrafiltration MP > NK1 > 100 ash > K3III24 P: Technological advantage of MP as mixture of strains (mixture of strains is needed)	4. 1. 2. 3.
2	Status of amino acids	
2.0	Production of amino acids NK1 > K3III24 > MP > 100 ash P: Low antagonism between certain strains within MP can be under consideration upon strain choice	1. 3. 4. 2.
2.1	Tyr (sites for serine proteinases, fluorophores) K3III24 > 100 ash > MP > NK1 P: Tyr can serve as criterion of utilization of fluorophores	3. 2. 4. 1.
2.2	Phe (sites for serine proteinases, fluorophores) NK1 > MP > K3III24 > 100 ash P: Support of point 2, revealing mechanism for point 2	1. 4. 3. 2.
2.3	Fluorophores (Trp, Tyr) (excitation at 254 nm) 100 ash > K3III24 > NK1 > MP P: Dominated contribution of Tyr and their derivatives	2. 3. 1. 4.
2.3.1	Fluorophores (excitation at 365 nm) 100 ash > K3III24 > NK1 > > MP P: Degradation/ utilization in MP (fluorophores cannot be used as targets)	2 3 1 4
2.4	Gly (hydrophobic, anti-adhesion action) NK1 > MP > K3III24 > 100 ash P: Gly as natural additive to improve signal activities and communications	1. 4. 3. 2.
2.5	Leu (hydrophobic, site for peptidases) (Parameter is slightly dependent on strain origin) K3III24 > 100 ash > MP, NK1	3. 2. ¼**. 4/1.
2.6	Ile (hydrophobic, participation in synthesis of biologically active volatile fatty acids) K3III24 > 100 ash > MP > NK1	3. 2. 4. 1.

No.	Parameters of supernatants, ranging MP and its strains, proposals (P)	Code ranging MP and its strains*
2.7	Ala (partially from peptidoglycans, site for exopeptidases) MP > K3III24, 100 ash > NK1 P: Antagonism between strains results in partial cell wall degradation in MP	4. 2/3. 3/2. 1.
2.8	Ser (sites for hydrolase splitting and O-glycosylation) MP > K3III24 > 100 ash > NK1 P: Support of point 1.4	4. 3. 2. 1.
2.9	Thr (site for O-glycosylation) NK1 > 100 ash > MP > K3III24 P: Thr as criterion for evaluation of metabolism of cluster square positions for recognition in proteins (in comparison to point 2.8)	1. 2. 4. 3.
2.10	Lys (from cationic poly/oligopeptides, site for serine proteinases, participation in *Maillard* reaction) MP > 100 ash > K3III24 > NK1 P: Support of point 1.4	4. 2. 3. 1.
2.11	Val (hydrophobic, participation in synthesis of biologically active volatile fatty acids) K3III24 > 100 ash > NK1 > MP P: Mostly important criterion concerning volatile fatty acids producing	3. 2. 1. 4.
2.12	Glu/Gln (also as sites for amidases) NK1 > MP, K3III24 > 100 ash	1. 4. 3. 2.
2.13	Asp/Asn (sites for amidases and N-glycosylation) MP, 100 ash > NK1 > K3III24 P: Partial support of point 1.4	4. 2. 1. 3.
2.14	His (participation in auto-oxidation of protein, high affinity to metal cations, activation of oxidases and heme) MP > NK1 > 100 ash > K3III24 P: Potential for metal chelate affinity chromatography and immobilization (for microassays)	4. 1. 2. 3.
2.15	Arg (from cationic poly[oligo]peptides, destruction during pigments forming in *Maillard* reaction) MP > NK1 > K3III24 > 100 ash P: One of the way of decolorization of MP	4. 1. 3. 2.
2.16	Met (antioxidant) NK1 > MP > K3III24 > 100 ash	1. 4. 3. 2.
2.17	Cys2 disulfide bonds (oxidation of SH-groups into Cys2) K3III24 > NK1 > MP > 100 ash[not observed]	3. 1. 4. 2.
2.18	Pro (Pro-bends in regular structures of proteins) 100 ash > MP > K3III24 > NK1[traces]	2. 4. 3. 1.
3	Status of biosurfactants	
3.0	Associated biosurfactants in complexes >27 kD NK1 > MP > > 100 ash > K3III24 P: NK1 as the main source of movable permeable (detergent like) complex effectors; support point 4.3	1. 4. 2. 3.
3.1	Biosurfactants active against mineral oil K3III24 > MP > 100 ash > NK1	3. 4. 2. 1.
4	Other parameters	
4.1	Emulsifiers 100 ash > NK1 > MP > > K3III24 [absence] P: K3III24 needs combination to any other strain to increase cultural components (>27 kD) to be emulsified	2. 1. 4. 3.

No.	Parameters of supernatants, ranging MP and its strains, proposals (P)	Code ranging MP and its strains*
4.2	Pigment products [optical density at 420 nm] K3III24 > NK1 > 100 ash > MP P: K3III24 as the main potential source of neoglycoconjugates of nonenzymatical origin; MP as maximally decolorized product needed cofunctioning strain mixture; partial inverse correlation to point 1.3	3. 1. 2. 4.
4.3	Antimicrobial activity (toward a panel of diagnostic mainly Gram-negative bacteria) MP > NK1 > 100 ash > K3III24 P: Support point 3; potential of K3III24 to other targets (against Gram-positive bacteria and fungi)	4. 1. 2. 3.

**1, NK1 (Lactobacillus helveticus NK1); 2, 100 ash (L. helveticus 100 ash); 3, K3III24 (L. casei K3III24); 4, multiprobiotic (MP) on example of variants of Acilact.*
***Alternative positions.*

Table 3.
Strain code ranging for multiprobiotic construction on example of Acilact (the Lactobacillus multistrain probiotic).

(maximal resulting hydrolytic activities in respect to acidic proteins; increased level of antimicrobial peptides), 1.2 (maximal resulting hydrolytic activities in respect to cationic proteins; increased level of antimicrobial peptides including bacteriocin-like), 1.5 (the minimal level of aggregation upon storing concentrates), 2.3 (the minimal level of fluorophores exciting at 254 nm; contribution of Tyr and Trp or their derivatives), 2.3.1 (the minimal level of fluorophores exciting at 365 nm; contribution of Trp); and 4.2 (the minimal level of colored products); the major ingredient strain contributors are accounted as the third position in code.

The third step: The final formulas (formulas of category C) include combinations of formulas A and B. Multifunctionality of parameters analyzed can be extended (as in cases of amino acids [25]).

Extended approach for constructing more adaptive mixtures of lactobacillar and bifidobacterial MP (on the basis of *Acilact* extended by accounting industrial bifidobacterial strains) is presented in **Table 4**.

As expected, taxonomically mixed probiotics (symbiotics) will possess increased survival in biotopes of human organism. The same principles and algorithm (as for formulas of *Acilact* variants described above) can be applied. Combinations of *Acilact* ingredient strains and ingredients of *Bifidin* (*B. longum* spp. *adolescentis* MS-42), *Bioprotectin* (*B. bifidum* No. 1), and other bifidobacterial probiotics produced in Russia are of priority interest (also due to the possibility of their usage as standard models).

Table 4 demonstrates algorithm of further passage from intra-genus cases (*Lactobacillus*) of Gram-positive MP to inter-genus cases of MP as combinations of probiotic lactobacilli and bifidobacteria of the human gut origin.

Selective sets of parameters (points in **Table 4**) indicate principle differences between lactobacilli and bifidobacteria (as blocks of lactobacillar and bifidobacterial strains in 7-mark code). Completing lactobacillar/bifidobacterial synergism is expected and predicted. Selected combinations of strains from both blocks can be used for creation of directed MP. Other more complex cases include unblocked lactobacillar and bifidobacterial sequences within the code (additional prognostic conclusions are possible). Code positions "1" and "5" (both strains produce high levels of cytoagglutinating LS) reveal adjacent/similar behavior that indicates high level of compatibility of the strains NK1 and MS42.

No.	Parameters of concentrate (C), their ranging, proposals (P)	Code ranging strains and MP
1	Antifreeze components >27 kD, pI 4–8 (against any type of crystal forming during IEF-PAG): gall > bif1 > MS42 > NK1 > MP > K3III24, 100 ash P: bifidobacterial C for stabilization of K3III24 and 100 ash	*7. 6. 5.* **1. 4. 3/2*. 2/3.**
2	Formation of organic crystals in the presence of components >27 kD (in conditions of 7M urea, 5% saccharose, 8°C, night, IEF in slab of PAG): pI 4–6: 3III24, 100 ash > MP > NK1 > MS > bif1 > gall (not) pI 6–8: K3III24, 100 ash > MP > NK1 > gall>bif1 > MS42 P: Potential approach to micro- and nanoassembling effectors	**2/3. 3/2. 4. 1.** *5. 6. 7.* **2/3. 3/2. 4. 1.** *7. 6. 5.*
3	Complex protein C > 27 kD: pI 4–6: NK1 > MS42 > K3III24 > gall> 100 ash > bif1 > MP pI 6–8: NK1 > gall > K3III24 > MS42 > 100 ash > MP > bif1 P: Donors of cationic bacteriocin-like associates with exopolymeric compounds	1. 5. 3. 7. 2. 6. 4. 1. 7. 3. 5. 2. 4. 6.
4	Adhesins as colorless transparent not water-soluble drops on polystyrene (number of drops): gall > MS42 > NK1 > bif1 > MP > K3III24 = 100 ash(not) P: The size and numbers of drops indicate level of emulsification of C compared to original supernatant	7. 5. 1. 6. 4. 2/3. 3/2.
5	Associated biosurfactants: bif1 > gall > K3III24 > MP > 100ash > MS42 > NK1 P: C "NK1 + gall" and "NK1 + bif1" as synergistic antimicrobials	6. 7. 3. 4. 2. 5. 1.
6	LSSM as mucin-binding: pI 4–5.5: gall > MP > NK1 > MS42 > bif1 > K3III24, 100 ash pI 5.5–8: MS42 > bif1 > gall > NK1 > MP > 100 ash, K3III24 P: C for delivery into intestinal and urogenital mucosal cavities	7. 4. 1. 5. 6. 2/3. 3/2. *5. 6. 7.* **1. 4. 2/3. 3/2.**
7	LSSM as mannan-binding: pI 4–5.5: 100 ash, K3III24 > NK1 > MS42 > gall > MP > bif1 pI 5.5–8: gall > bif1 > MS42 > NK1 > MP > 100 ash, K3III24 P: Potential against eukaryotic (yeast and yeast-like), prokaryotic (staphylococci), and HIV/HIV-related infections; delivery into cell and cell organelles	2/3. 3/2. 1. 5. 7. 4. 6. *7. 6. 5.* **1. 4. 2/3. 3/2.**

*1, NK1 (L. helveticus NK1); 2, 100 ash (L. helveticus 100 ash); 3, K3III24 (L. casei K3III24); 4, MP (Acilact); 5, MS42 (B. adolescentis MS42); 6, bif1 (B. bifidum No. 1); 7, gall (B. gallinarum GB); C, concentrate (>27 kD) of cultural fluid supernatant; IEF, isoelectrofocusing; PAG, polyacrylamide gel; P, prognostic proposals; *Alternative position. Blocks of lactobacillar (**boldface**) and bifidobacterial (italic font) strains are shown.*

Table 4.
Strain code ranging for multiprobiotic construction on example of new multiprobiotics including bifidobacteria and lactobacilli.

Further constructing other or extended multistrain symbiotics is depended on choice of important parameters of interest (to increase the number of comparable codes used in **Tables 3** and **4**). Important prospects in constructing taxonomically mixed symbiotic formulas are expected on the basis of identified LSSM sets of the strains as counted ingredients of multisymbiotic as well as evaluation of the relative contribution of LSSM types in resulting multifunctional activities of mixed product. For example, the general properties of LS of lactobacilli and bifidobacteria investigated by us are "recognition of mucin-type targets" more or less than "recognition of mannan-type targets" for LL or BL, respectively [8]. As a result, LSSM-dependent synergism (which can be directed and predicted using extended panel of GC for LSSM selection and choice) of new taxonomically mixed symbiotics can be achieved.

Universality of approach proposed in **Table 4** means that the panel of comparative parameters of investigation is unlimited for selection. As advantages of this approach for creation of perspective formulas of multipro-/symbiotics, some properties of future combinative products can be predicted and verified.

Aforementioned codes (**Tables 3** and **4**) extend the potential of using traditional MP. Results open new possibilities for investigation of LSSM types among strains and constructed consortia to develop perspective GC-type-dependent LSSM combinations possessing needed actions toward human interactome. In terms of personalized medicine, individual LSSM applications are of reality. For example, LSSM could be applied as "a functional tissue biotope" or mucosal organ-specific agents and organizers of lectin-coupled reactions and activities [26, 27].

3.3 Anaerobic synergistic preparations containing LSSM for support of human protective systems

Due to high distribution in organism, oxidative stress (as the power destructive factor initiating diseases) needs the constant presence of the power protective antioxidant systems [28, 29]. Some therapeutic proteins regulating cellular consumption of oxygen can be involved into development of tumor and other side pathologies in organism. We isolated system anaerobic (without oxidases initiating of oxygen and peroxide radicals) preparations of acidic/anionic and alkaline/cationic LSSM from cultures of symbiotic (probiotic) industrial strains of human bifidobacteria and lactobacilli as consortia that were successfully applied. Such preparations devoid the ability to induce destructive oxidative stress (cross-linking and inactivation of therapeutic proteins, etc.) in respect to surrounding infrastructures.

The used synthetic GC in our work were characterized with antioxidant properties in respect to LS as carriers of GC (prolongation of chemiluminescence of protective complexes was observed). Similar resulting protection of LSSM was also registered in the presence of neutral and cationic bifidobacterial and lactobacillar cultural exopolymeric compounds (EPC) of nonprotein origin (as observed on the blot after IEF-PAG). Acidic and alkaline anaerobic LS of bifidobacteria and lactobacilli revealed the following general antipathogenic actions: (a) own and overlapped/synergistic; (b) toward communicative bodies of microbial massifs and biofilms of the potentially pathogenic yeast-like fungi and Gram-positive bacteria. All four types of preparations of LSSM used were characterized by own mechanisms of antimicrobial actions in comparison to action of other antimicrobial systems (antibiotics, bacteriocins, phytolectins, subisotype products of isotypes C4B and C4A of the human complement component C4) [30, 31]. LS from human probiotic bacterial cultures revealed the ability to act as cascades in such reactions as initiation/changing or switching recognition of GC of different types (imitators of mannans, mucins, components of bacterial walls, Forssman antigens, Tn, blood group substance A) using the same original pool of lectin forms of taken multistrain probiotic. The presence of cations Ru^{2+} (ingredient of SYPRO involved in photosensibilization) strongly increased discreteness and number of forms of acidic lectins—potential carriers and deliveries of GC. Stability of obtained mosaic asymmetric landscape pictures of the systems LSSM-GC as multistrain probiotic-depending and multistrain probiotic-supporting biotope balance of recognition and reversible retaining/depositing of GC (therapeutics, biomarkers, others) was observed. Combinations of anaerobic LS-containing proteins revealed themselves in respect to yeast-like and Gram-positive pathogenic targets as more selective in the choice of the adequate regional territory of massif of pathogen and limitation of early and late time (depending on localization of targeted region of communicative

body of pathogen) for the mostly effective visible actions of LS, obtaining uniform pure landscapes of LSSM action on massif of *Candida albicans* (the absence or minimization of LSSM-resistant residual fungal colonies in the interacting intestine system "LS of human intestinal bifidobacteria and lactobacilli—human intestinal *C. albicans*"). Antimicrobial activities of LSSM and phytolectins (phytohemagglutinin from the kidney bean) could be realized not only directly but also through the influence (together with synthetic mannans and mucins) in respect to macrophage migration as well as through inducing production of cytokines by stimulated blood lymphocytes (on the example of tumor necrosis factor-α). Results indicate prospects of anaerobic LSSM as assistant ingredients of the possible drug forms.

3.4 Synbiotic minibioreactor using LSSM for screening GC

During the last time, synbiotics and symbiotics (as synergistic sum of probiotics and prebiotics) are of increased investigator interest due to their antimicrobial and other useful reactions [1, 2]. In this respect LSSM represent new class of antipathogenic proteins (possessing extended potential of application) which recognize different GC. LSSM represent multifunctional potential of relatively highly molecular mass polymeric metabolites of cultures of the human microbiota (microbiocenoses) and consortia (also multistrain probiotics) of human indigenous microorganisms. LSSM cofunction together with artificial and biologically active natural GC [32].

According to own results, we proposed suitable laboratory minisystem for screening prebiotic and therapeutical GP using LSSM and sterile heparinized insulin syringes of 1 ml volume. The following results were obtained: (1) LSSM-containing fraction stimulated production of both the whole and adhesive mass of bifidobacteria, (2) LiCl (15 mM and higher) increased dose depending on the number of adhesive colonies, (3) bifidobacterial LSSM (within pI 4–4.5) were characterized with strong affinity to anionic synthetic GC (possessing exposed residues of sulfated galactosides or, in a less extent of affinity, exposed residues of mannose-6-phosphates), and (4) sulfated glycosaminoglycans together with cations Li^+ and LSSM as potential carriers of Li^+ participated in functioning bioreactor imitating synbiotope (multiplication of bifidobacterial colonies and their survival were observed).

Proposed synbiotic system is perspective for screening prebiotic GC (as it is known for prebiotic derivatives of chitin, chitosan, fucoidan, and glycopeptides [33, 34]). **Table 1** includes potential prebiotic sources such as chitin and α-L-fucan which react to LSSM (LSSM may serve carriers of metabiotic GC; the list of GC can be unlimitedly extended).

3.5 Membrane technological prospects of LSSM

Progress in membrane and solid-phased technologies using LS-GC interactions includes the potential of their application in microassays, biochips (membrane bound glycoarrays or lectin arrays), and biosensors [35, 36].

The use of affine pore hydrophobic (uncharged) membranes predictably covered with mosaics of multifunctional sets of LSSM (additional significant purification of LSSM on membranes is reached) allows prolonged storing LSSM without decreasing samples in activities. The following prospects of LSSM-GC combinations may be of practical interest: (a) antifungal covers of prolonged action in combination with antibiotics and physical factors of stress [radiation (ultraviolet and ultrasonic), light (biorhythm "day-night"), temperature, pH, oxygen, season changes (also biorhythmic), others] and (b) chemiluminescent systems cofunctioning in regime of real time for medical and industrial biotechnology and

bionanotechnologies [our results include the following coupled systems: "low acidic LSSM, low acidic oxidoreductases of lactobacilli"; "alkaline bifidobacterial LS, alkaline bifidobacterial exopolymeric compounds"; "neutral lactobacillar/bifidobacterial LS, neutral lactobacillar/bifidobacterial biosurfactants"; "LS, strongly acidic (pI 3–4) serial phyto-oxidoreductases/phyto[glycosyl]oxidases"].

Membrane technologies using separated proteins, oligopeptides, and their complexes (especially) together with intrinsic or exogenic (SYPRO dye) fluorescence registered in live bioimagination are especially sensitive and perspective (protein band discreteness using fluorescence technique was better compared to the chemiluminescence technique). The latter allows identification stabile boundaries of the whole protein massifs for further establishment of LSSM and other biologically and physiologically active components among protein mosaics. Bioluminescence (fluorescent technique in combination with chemiluminescence technique) in optimal (depending on the object and the goal of study) conditions allows express-ranging cultural fluid groups of proteins and LS according to molecular mass (for additional standardization and typing of strains), evaluation of interstrain synergism and contribution of protease and oxidoreductase systems of mono- and multistrain probiotics (symbiotics) and other type consortia, and identification of mosaics of complexes containing fluorochromes in extended interval of pI/pH (complexes and cell wall fragments as carriers of visible energy which is ready for energetic exchange with surrounding infrastructures as well as for monitoring directed supramolecular assembling and their reorganization).

Aforementioned data presented develop other possible important prognostic approaches and proposals. The choice of wished prognostic (LSSM-selected-type and GC-type interactions)-directed events in biotope can be determined and regulated by involving GC types needed (panels of natural and artificial GC used in biotope; extending the list of GC indicated in **Table 1** is possible). The use of artificial polymeric GC with established chemical structures allows receiving adequate, understandable, and reliable results.

According to the multifunctional potential of artificial GC used, resulting events in biotope can be the following ones: antipathogenic actions (the use of GC-imitating pathogenic cell surface structures), prebiotic and symbiotic (synbiotic) actions (the use of GC-imitating prebiotic structures), increasing own human organism protective systems (the use of GC-interacting and GC-regulating macrophages and macrophage-like lymphocytes through their systemic receptor lectins), antitumor actions (potential using antigenic GC together with LSSM as antagonists and synergists in intercellular antitumor and anti-infectious communications [37]), and cytokine lectin/lectin-like cascades initiated/regulated with LSSM potentially influencing redistribution of cytokine network in organism.

3.6 Prospects of LSSM for prophylaxis and therapy of infectious diseases

Innate immunity plays an important role especially when antibody immunity is under development, suppression, or alteration. So the search of new natural anti-infectious agents is of actuality. In contrast to probiotic cells, LSSM (as systems of LL or LB) are not sensitive to the presence of antibiotics and chemotherapeutics as well as do not need special conditions for survival. LSSM function as metabolomebiotics according to the principle "the network in the network"; participation of major lectins in supporting physiologically significant glycodecor of biotope mucosal probiotic compartments, and minor lectins—in signal communications; support of such compartments (compensation of the absence of probiotic cells in MB upon therapy with antibiotics, delivery of fucosylated and galactosylated prebiotics of mutual supporting influence between populations of bifidobacteria and lactobacilli,

cofunctioning to anti-infectious agents (antibiotics, metabiotics, GC) and cells of organism protective systems (macrophages and leukocytes).

We characterize LSSM (acidic, low acidic, cationic: aLL, laLL, cLL, aLB, and cLB) of domestic probiotics which recognize polymeric artificial GC mucin-like analogs of antigens and EPC (fungal and bacterial mannans, bifidobacterial α-L-Fuc-containing, sulfated and phosphorylated).

Antimicrobial directions of LSSM action were established [26, 31, 38].

3.6.1 Anticandidosis activities

- Against intestinal and urogenital *Candida* of epidemiologically significant species of group I (*C. albicans* and *C. tropicalis*: early action of aLB within the first 2 days; delayed action of cLL and LB within 1–2 months; synergism between acidic and cationic LSSM, cLB, and grass lectins, aLSSM/cLSSM, and some antimycotics)

- Against *Candida* of epidemiologically significant species of group II (*C. glabrata*: inhibition of virulent factors such as fungal IgA1 and IgG proteinases, EC 3.4.21.72 and EC 3.4.21., respectively [9])

- Against *Candida* of epidemiologically significant species of group III (*C. krusei*: delivery of potential effector GC on cell surface)

- Interruption of mycosymbiosis parasitism of *Candida—Aspergillus*: the drugs against candidosis as predictably affective against aspergillosis)

Activities of LSSM against staphylococci (on example of patients *S. aureus* isolates): aLL > aLB; aLL and aLB; LSSM activities accompanied with:

- Delayed degradation of microbial massifs

- Partial directed lysis of microbial massif

- Tearing away fragments of massif (by two mechanisms depending on lectin type)

- Synergism between aLL and LB in antistaphylococcal actions

LSSM possess potential of diagnostics and prognostics of biotope diseases [37]. Results support important principle approach that diseases of MB (as in the case of CBF according to the principle "there is the body—there are diseases") reflect own "biotope diseases" in organism [39]. LSSM can be used in phenotyping prognostics and diagnostics of infectious processes in organism; for prophylaxis and therapy of candidoses, staphylococcoses, mixed fungal-bacterial infections, mixed symbiotic mycoses; innate infections; immunodeficiency and infections against the background of immunodeficiency, upon antibiotics-/chemo-/radiotherapy. Such GC effectors as metabiotics, prebiotics, glycoantigens, and drugs of selective directed action are of availability.

It is of importance to consider the participation of LSSM in supporting biotope mucosal MB in conditions of oxidative stress (cofunctioning of laLL and probiotic oxidoreductase systems) [26]. Panel combinations of LB and LL are perspective in early evaluation (before the inflammation) of status of MB of functionally different biotopes of the vaginal tract.

LSSM are similar (in specificities, systemic action) to communicative lectins of intercellular reception in innate immunity.

LSSM act as essential part of human protective supersystem (the supersystem with probiotic type action) [31]. Such supersystems contract disturbing the balance of the body's health processes; keep and maintain the integrity of biotope microbiocenoses like healthy consortia. There are supersystems with antimicrobial or antifungal action in organism.

3.7 Potential of results for innovations

Results obtained by us in a study of probiotics can be useful as a set of approaches in study of the following aspects of clinical microbiology and medical biotechnology (in brackets—significance and prospects of results for infectology) [40, 41].

3.7.1 Metabolite technologies

- Cultural metabolites 27–200 kD within pI 4–8 (separation of acidic and alkaline protein and nonprotein of taxonomically significant systems); phenotyping of strains in cationic region containing protected sets of proteins Subcytoagglutinating activities: initiatively coupled or non-coupled to lectin and cytoagglutinating activities (cytokine activities; synchronization of cultures for increasing vulnerability of pathogens; typing).

- Functional blotting analysis of cascade cultures in combinative nutrient media (NM) (as in the case of milk followed by transfer into "casein hydrolysate-yeast autolysate" media; monitoring lectins, enzymes, and exopolymeric compounds [EPC])

- Development of strain-supporting NM (comparison of blotted maps of components of cultures in identical conditions)

- The use of α-S-, β/γ-, and kappa-caseinases (increase of effectiveness of NM, accumulation of physiologically active protein and nonprotein metabolites and their complexes)

- Systems of proteinases, EPC depolymerases, and/or peroxidase-like catalases in cultures (revealing strain-dependent producers of enzymes, proteins, and EPC; evaluation of cytolysis populations, oxidative stress, virulent factors, changes, and aging of cultures upon passages and storage)

- Lectin systems: major and minor, building and signal, *cross talk* and *quorum sensing* (standardization of cultures and analysis of communicative networks) *Evaluation of early and prolonged landscape synergism of recognizing components of cultures and antibiotics (individual choice and replacement of combinations of probiotics and antibiotics upon therapy of patient)

- Natural and recombinant systems oriented to recognition of polyvalent glycoconjugate targets of known structure (standardization of strains; monitoring and revealing signals of carbohydrate metabolism)

- Imitation by cultural metabolites in respect to strain or consortium effectiveness (standardization of strain multifunctionality)

- The use of recognizing metabolites instead of cells or in combinations with cells for support of feeble living and antibiotic-sensitive cultures (also in cases of non-culturable microorganisms).

- Constructing balanced supporting MB of probiotic cell-metabolite consortia (constructing symbiotic consortia, balanced vaccines)

3.7.2 Intercellular and cell-metabolite technologies

- For Gram-positive bacteria (opportunistic and pathogenic)

- Sensor microbial systems of MB (revealing and using key antagonistic systems) Directed assembling of cytokine-cell gradients: reversible functional (1–2 days) or late irreversible conserved and partially inactivated (4–6 weeks), as in cases of biofilms containing erythrocytes—in microassay (evaluation of protection and degradation of human cells in the presence of pathogens)

- Biofilm forming as ranked quantitative and qualitative, early and delayed—in microassay (reactions of mono- and mixed biofilms)

- Species-dependent redistribution of antagonistic MB (prediction of mutual influence between species and strains of probiotics, opportunistic microbes, and antibiotics)

- Leader strains and species within MB (evaluation of temporary MB-destabilizing strains in coexistent antagonistic microbial populations)

- Destabilization and synchronization of MB by recognizing components of cultures for increasing future selective synergistic action of antimicrobials and stress factors (increase of early and late suppression of pathogens) Microecological interniche early and delayed landscape relationships in cases of solid-phased and suspension microbial massifs, for microanalysis (evaluation of opportunistic microbes and MB as communicative bodies opposed to mosaics of antimicrobials)

- Construction of active (involving probiotic leaders) and stabilizing (species-dependent and resistant to antibiotics, probiotic-like supporting MB) consortia (using upon therapy)

- Strain-phenotyping dysbiotic MB using lectin systems (revealing early changes in patient MB in the presence of lectins of MB, for development of new strategies of therapy)

- LS of probiotic consortia (directions of consortium formula actions can be predicted by constructing) as ingredients of functional food to support resistant functioning mucosal organs

4. Conclusion

The data presented consider aspects of constructing probiotic multistrain intra- and inter-genus Gram-positive bacterial metabolites on examples of bifidobacteria and lactobacilli of the human gut origin. Algorithms of creation

of 4- and 7-code MP formulas are presented and argued. It is of importance to consider LSSM and their GC as a new perspective protective basis/scaffold factor influencing and supporting human interactome, involving biotope infrastructures, signaling, and anti-infectious actions as well as cofunctioning together with other protective human systems [17, 42]. Results support the use of pro-/symbiotic LS as assistant-coordinated metabolomic agents; carriers for delivery and releasing GC, metabiotics (including simulators of cell surface patterns of opportunistic microorganisms), prebiotics, therapeutics, and antigens (for cofunctioning to antibodies); and reserves for decoration elements that support stabile functioning landscapes of the human cell surfaces and mucosal tissues. Probiotic lectins (interacting with synthetic GC simulators) are important for screening, typing, and selection of useful strains and their consortia supporting organs. The proposed LSSM-containing preparations promise LSSM using a soft adaptive multidirected network synergistically acting together with other protectors (also in conditions of the absence of oxygen [involving oxidative stress and forming of covalently bound by-products] within biotope). Variants of multipro-/sym-/synbiotics constructed can be perspective for prophylaxis for individuals and contingents as well as for supporting treatments of patients (before and postoperative period, during chemotherapy, etc.). Approaches developed are useful in study of interniche relationships of extended set of Gram-positive and fungal microorganisms in mono- and mixed cultures. Procedures can be applied in different fields of clinical microbiology and medical biotechnology.

Conflict of interest

The authors declare the absence of conflict of interest.

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