POSTBIOTICS AS FACTORS AGAINST DISEASES ALONG METABOLIC AXES

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Abstract. The review represents an analysis of recent year publications in connection with preventive and therapeutic use of postbiotics (PB). Postbiotics are widely used as immunomodulators, anti-inflammatory agents, protectors and the normalizers of metabolism of the open cavity mucosal biotopes, liver, brain and other organs, tissues and innate immune cell populations that co-function to intestinal microbial metabolites as a network (co-function within a number of metabolic axes “intestine-other locations”). They act in combination with other effectors as auxiliary agents prolonging the effect of drugs and supporting them. Prophylactic and therapeutic uses of PB are directed against groups of intestinal infection diseases, hepatitis, tumors, neurodegenerative brain disorders, other metabolic disorders and pathologies. New aspects of research of PB include the study and application of recognizing and binding therapeutic PB according to and in connection with a network of “Probiotic lectins—Glycoconjugates” interactions. The data indicate the prospects of a search and application of the new groups and combinations of PB directed at glycoconjugate exposed targets in accompanying and supportive therapy. Probiotic bifidobacteria, lactobacilli, baker’s yeast and probiotic lectins are perspective resources of synergistic sets of metabolite-cellular PB against diseases, pathologies and groups of infections.

Аннотация. В обзоре приведен анализ публикаций последних лет в связи с профилактическими и терапевтическими перспективами применения постбиотиков (ПБ). ПБ широко используются как иммуномодуляторы, противовоспалительные агенты, протекторы широкой направленности и стабилизаторы нормального метаболизма мукозальных биотопов и функционально связанных с ними печеней, мозга, легких и других органов и тканей, а также популяций клеток с защитными и коммуникативными свойствами врожденного иммунитета. ПБ действуют в сочетании с другими эффекторами как вспомогательные, дополняющие, синергистические, пролонгирующие действие лекарств и поддерживающие статус здоровья метаболических осей, функционально соединяющих микрофлору кишечника с другими органами и тканями. Профилактическое и терапевтическое действие ПБ направлено против кишечных инфекций, гепатитов, опухолей, нарушений жирового обмена, нейродегенеративных болезней, других патологий. К новым направлениям исследования и применения ПБ относится изучение распознающих и связывающих гликоконъюгаты ПБ с множественным профилактическим и терапевтическим потенциалом. Приведенные данные указывают на перспективность применения ПБ с профилактической целью и в сопроводительной терапии. Мишенями ПБ могут быть функционирующие макросостоящие интерактома - метаболические оси. Пробиотические микроорганизмы, а также имитирующие их пробиотические лектины, остаются перспективными источниками новых синергистических метаболитно-клеточных наборов ПБ против групп инфекций, патологий и болезней.

Keywords: postbiotics, prebiotics, probiotic lectins, pathologies, diseases, prophylaxis, therapy.

Ключевые слова: постбиотики, пребиотики, пробиотические лектины, патологии, болезни, профилактика, терапия.

Abbreviations
GC : Glycoconjugates
PB : Posbiotics
Introduction. Postbiotics (PB) include non-living microbes and their products, metabolic by-products of the vital activity of pro/symbiotic microorganisms with the manifestation of beneficial biological and physiological activities at all levels of the host organization. PB may represent soluble factors as a result of the metabolic activity of living microorganisms, as well as identified molecules that can directly or indirectly provide benefits for maintaining and enhancing health. PB mimic the activity of living cells and may exhibit properties alternative to cells. PB exhibit such important characteristics as a safe profile, a longer shelf life, resistance to mammalian enzymes (including PB are considered as end products of enzymatic hydrolysis) and stability of activity in the digestive system [1-4]. PB can include predominant metabolites of microorganisms of varying degrees of purification (including secreted from cells and cell surface, modified and characterized by chemical structure of (glyco)(lipo)peptides and their complexes). PB can also be products of cell walls (their fragments, peptidoglycans and proteins, including those subject to hydrolysis and extraction into the environment in the presence of detergents, physico-chemical and biochemical factors, including as a result of stress).

Interest in PB is high not only due to the broad prospects of an industrial nature (use as promoters of animal growth, strengthening their health), but also due to the potential for the use of PB in reducing the risk of a wide range of infectious and other human diseases and pathologies, creating additional conditions for the body's immunity to infections, as well as due to the need to establish systemic mechanisms for prevention and therapy. Currently, PB is widely used as part of formulas for therapeutic and baby food (categories of children and patients) and fermented phyto- and animal products (including with the use of specifically directed combined fermentation), and the range of PB used in practice is steadily expanding.

The purpose of the review is to assess the current potential of PB in the correction of diseases, metabolic disorders and other pathologies, including microbial and viral nature.

Areas of PB research

In the metabolic axes:

*First of all, metabolic axes within frames of the mucous open cavities of the body (between parts of the intestine [ileum, colon, caecum, other departments], "Intestinal tract—Urogenital tract", "Intestinal tract—Oropharynx") are requested in connection with multiple action of the PB.

*The metabolic axis "Intestine-Liver" [5]. The targets of this type are functionally linked intestines and liver (the resulting vector of action is directed from the intestine to the liver). This aspect is noted in most publications on effects of PB on diseases (mainly on examples of the intestines and liver), reflects an increase of the established role of PB in strengthening mucosal immunity.

* The “Gut-Brain” axis reflects the importance of combinations of PB in targeting a metabolic axis (metabolic-axial relationships as targets and objects of therapy) [6, 7].

*The "Intestine—Adipose tissue as an organ” axis. PB can reduce the side effects of obesity.

*The "Intestine-Lungs” axis. The effects of PB on respiratory syncytial virus (RSV)-induced events, secondary pneumococcal pneumonia are indicated [8].

*The "Gut-Skin” axis. PB with a general health-improving effects: in atopic eczema, atopic dermatitis, hair growth disorders – all of the potential to eliminate cosmetically significant deficiencies and defects [9, 10].

Other direction proposed:

*From the empirical multi-action of the probiotic supernatants - to the identification of the contribution of mono/bi/multi-components of isolated and characterized PB, including by establishing the chemical and spatial physical module structure.

*Construction of new PB and their combinations using directed predictable specific fermentation by (or in the presence of) probiotic bacteria and their consortia (for example, selected by two species [L. casei CRL 431 and Bacillus coagulans GBI-30], six strains of the same species [L. plantarum]) [11-13] can be used as examples.

*The use of bacterial cell walls and their components as PB and prebiotics (including proteoglycans and proteins) is of special interest to be developed [8, 9, 12, 14-18].

*Combination of PB and prebiotics (including inulin derivatives and other compounds) [6, 19, 20].

*PB and their combinations in the prevention and treatment of groups of similar diseases and pathologies (including with simultaneous positive effects), systemic primary and secondary diseases (including cardiovascular and autoimmune disorders).

*Expansion of groups of studied diseases when using one type of PB for detailing and further standardization of this selected/ preferential PB.

*Unlimited expansion of the taxonomic and strain composition of PB sources with multi-action, as in case of Hilak Forte and Daigo [21, 22].

*Transplantation of intestinal microbiomes as unlimited sources of combined PB [23].

*Study and application of eukaryotic (mainly of yeast origin) PB [5, 24, 25]. Expansion of the taxonomic composition of PB sources with the transition to the level of eukaryotic PB.

*Synergistic mixed sets of PB and phytobiotics [26].

*Large-scale use of PB metabolism of Trp (indole and its derivatives) [27-31], the potential of Acylact cultures and its strains as sources of Trp [32].

*The use of PB against diseases involving protozoa [33].

*Study of the effect of PB on viral diseases [8, 34, 35]. Examples of rotavirus (RV) diarrhea, viral hepatitis and viral (RSV) pneumonia.

*The use of PB in connection with tumor resistance [3, 12, 36].

*PB in connection with diseases of growth disorders, the use of antibiotics (PB in weight control of industrial animals, instead of subdoses of antibiotics,
against antibiotic-induced diseases); substitution of antibiotics for PB as promoters of animal weight; the use of PB to solve the problem of obesity of individuals [15, 25, 37-39]).

*New PB system groups: Probiotic lectins recognizing GC as conversion sources of the potential therapeutic PB [14, 22, 40-42].

*PB against oxidative stress in tissues and organs in regulation enzymatic antioxidant systems of blood, intestines and liver [43].

*Combination of PB with innate immunity factors (cytokines, cytokine-like proteins and peptides), phytobiotics [26, 44-50].

*Search, development and application of PB in connection with childhood diseases [8, 50, 51].

*Development and application of PB as components of functional nutrition and in connection with food allergies [4, 11, 39, 52-54].

*Development and application of PB in connection with obesity.

*Development and application of PB in connection with the problems of gerontology [37, 50]: - expansion of the functions of immunity - the communication network of the body; - strengthening of antagonistic pathogens and pathogenesis factors of biotope infra- and signal functioning structures, participation in the creation of highly resistant (as a result of auto-selection processes) relationships to pathogenic factors of the PB network and body protection systems; - multivalent compensation by the PB network for the insufficiency of antibody protection.

*Medical biotechnologies of PB design: - at the levels of application of cell walls and their controlled fragmentation [9, 16]; - based on GC with a known varying/modified structure [19, 48, 55]; - based on micro/nano-particles and vesicles (including chemically modified ones) as carriers of PB [31, 47, 56].

*Consideration of vaccines in connection with the multi-action of PB [48, 56]: - surface cell proteins of Gram-positive bacteria as communication ingredients of vaccines; - vaccines in connection with immunomodulatory actions of PB; - PB in the conditions of vaccine action (maintenance of natural background metabolic surroundings);

- vaccines as GC-containing functionally coupled components, including those acting with the participation of GC-recognizing PB protection.

Table 1 systematizes data on the use of PB in the prevention and treatment of infectious and other type diseases and pathologies of humans and animals, as well as data on the multi-directional effects of PB on metabolic processes in the body.

Table 1. PB in action against pathologies and diseases of human and other mammals.

Diseases and pathologies (axis of action, localization, nature of the pathogen); sources of PB (taxonomic, molecular, others); activity and results; references.

**Intestinal diseases:**

*Diarrhea, pharyngitis, laryngitis, other diseases of the gastrointestinal tract (gastrointestinal tract) of children; PB from L. reuteri; prevention and treatment [51].

*Necrotizing enterocolitis (NEC), other diseases of intestinal inflammation (IBS); PB from L. reuteri, other lactobacilli; modulation of retinoic acid imprinting of mucosal dendritic cells (DC) [1, 2, 57, 43].

*Subclinical necrotic enteritis (SNE), ileum lesion caused by clostridia; PB of hydrolyzed extract of the yeast wall of S. cerevisiae, in combination with Lactobacillus spp. and Bifidobacterium spp.; antibiotic-comparable control of the microbiota of the cecum of broilers [24].

*SNE, hepatitis; PB and prebiotics of lactobacilli (L. johnsonii BS15, L. acidophilus, L. plantarum, others) and yeast S. cerevisiae cell wall extract; weakening of SNE, an alternative to antibiotics control of the intestinal microbiota of broilers [24, 25].

*Intestinal salmonellosis (diarrhea, fever, abdominal cramps and vomiting): L. rhamnosus GG supernatant; protection of mice [53].

*Post-infectious syndrome IBS; PB L. casei DG; decreased inflammation of the organ mucosa in ex-vivo culture against the background of increased expression, IL1-alpha, IL6, IL8 and TLR4 [3].

*IBS: PB L. rhamnosus GG; prevention of the epithelial barrier in enteroids and colonoids of the intestine from dysfunction induced by interferon-gamma and fecal supernatant in patients with IBS [58].

*Chronic inflammation of the gastrointestinal tract, cases of IBS; PB of lactic acid bacteria; combined multi-action [59].

*Varying diseases of the human gastrointestinal tract; microbiome PB; combined treatment with antibiotics [60].

*Varying diseases of the gastrointestinal tract of broilers; PB of lactic acid bacteria; immunomodulatory effect, weakening of the pathogenesis of the disease before treatment [61].

*Crohn’s disease (chronic granulomatous inflammation of the gastrointestinal tract, affecting all its departments), turning into cancer; new functional PB in the diet; correction of dysbiosis [52].

*Rotavirus (RV) diarrhea of suckling rats; PB of specifically fermented milk concentrate in combination with prebiotics; protection against diarrhea when milk feeding is impossible [34].

*Enteropathy of mice caused by nonsteroidal anti-inflammatory drugs (NSAID); indole of microbial nature in combination with indomethacin; significant reduction in pathology of the intestinal mucosa [27].
*Broiler dysbiosis; synergistic sets of PB and phytobiotics; support of intestinal microflora [26].

*Broiler dysbiosis; PB L. plantarum RG14 (PB RG14) in combination with a prebiotic (inulin); instead of antibiotic growth promoters and for directed cytokine expression in the ileum [62].

*Dysbiosis associated with antibiotic-associated disorders; intestinal microbiota PB as new pharmacobiological products; improvement of intestinal health [37].

*Dysbiosis; PB catabolism Trp; improvement of health [63].

*Food allergy and dysbiosis due to rainbow trout disease caused by L. garvieae lactococci; PB as new fermented lactobacillus species foods in the diet; prevention of the development of lactococcal infection [4, 11, 54].

Liver diseases (the "intestine-liver" axis):

*Hepatitis; indole of the intestinal microbiota; partial elimination of liver inflammation [28].

*Hepatitis; PB and transplanted fecal microbiota; immunomodulation [23].

*Steatohepatitis (fatty liver dystrophy) of rats; inhibition of intestinal dysbiosis and the withdrawal of endotoxins (lipopolysaccharides of Gram-negative bacteria) into the liver to weaken steatohepatitis [29].

*Acetaminophen-induced hepatotoxicity leading to acute liver failure in patients; (PB L. fermentum)-induced autophagy; weakening of the disease manifestation [65].

*Viral hepatitis cirrhosis; intestinal microbiota PB; attenuation of disease manifestations [35].

*Non-alcoholic fatty liver disease (NAFLD) or fatty liver disease associated with metabolic dysfunction (MAFLD); intestinal microbiota PB; noticeable positive effect [66].

Diseases of the nervous system (the "gut-brain" axis):

*Meningitis and sepsis in newborns (systemic E.coli K1 infection with the participation of poli-Sialo-capsular polysaccharide antigen K1, protecting against immune attack); PB of the L. rhamnosus GG supernatant; acceleration of the development of intestinal protection [67].

*Multiple sclerosis (chronic, autoimmune); indole-3-propanoic acid of the intestinal microbiota; inhibition of intestinal dysbiosis and the withdrawal of endotoxins (lipopolysaccharides of Gram-negative bacteria) into the liver to weaken steatohepatitis [29].

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*Multiple sclerosis (chronic, autoimmune); indole-3-propanoic acid of the linureneine pathway of Trp metabolism; potential effect [30].

*Parkinson's disease (similarity to the inflammatory process COVID-19); PB in combination with pharmacobiotics; positive potential of PB [68].

*Signs of depression in rats; PB to alleviate symptoms of depression through modulation of the Brain–Gut–Microbiome axis [69].

*Other disorders (neurodegenerative, neurodevelopmental and psychiatric), including against the background of intestinal dysbiosis (chronic inflammation); PB and prebiotics of the intestinal microbiota; influence through the "gut-brain" axis [6, 69].

Diseases of the pulmonary system (the "intestine-lung tissue" axis):

*Infection of respiratory syncytial virus (RSV), secondary pneumococcal pneumonia in mice; peptidoglycans of L. rhamnosus; improvement of childhood resistance to viral infection and pneumonia [8, 70].

*Immunocompromised patients; immunobiotic L. rhamnosus CRL1505 peptidoglycan; PB in connection with vaccines [70].

*Tuberculosis (M.tuberculosis); positive potential of PB as simulators of symbiotic microecosystem [71]

*Postcovid (COVID-19) syndrome as the progress of existing diseases and pathologies; PB as risk reduction factors for diseases and pathologies [72, 73].

* COVID-19 (similarity to the inflammatory process in Parkinson's disease); PB in combination with pharmacobiotics; positive potential of PB [68].

Skin diseases (the "gut-skin" axis):

*Cutaneous eczema and atopic dermatitis; positive effect of PB [9]. There is a cosmetic aspect of the use of PB in hair loss [10].

*Wounds on rat models; PB in creams; pronounced effect of PB on wound healing [74].

Pathologies associated with obesity (the "intestine-adipose tissue/organ" axis):

*Obesity (including excess of brown fat and brown adipocytes); PB (acetate, others) and prebiotics (including highly esterified pectin); in adaptive thermoregulation of fat consumption [19, 20].

*Obesity due to diabetes; muramyl-dipeptide-baed PB; reduction of obesity-induced insulin resistance [55].

*Obesity and type-2 diabetes, causing cardiometabolic diseases; varying PB of microorganisms; positive effect [75].

*Non-alcoholic fatty liver disease (NAFLD) or fatty liver disease associated with metabolic dysfunction (MAFLD); intestinal microbiota PB; registered positive effect [66].

*Obesity on the background of intestinal dysbiosis; intestinal microbiota PB; elimination of dysbiosis [76].

Other diseases and pathologies (axis "intestine-other organs and tissues"): PB microbiomes of the intestine, skin, urogenital tract and oral cavity in the biocontrol of diseases and other pathologies [77].

*Reduction of insulin resistance (an auxiliary pathway to diabetes control) [55].

*Diabetes mellitus; PB; positive outcomes [78].

*Intestinal amoebiasis (amoebic dysentery); Lactobacillus PB; inhibitory effect on Entamoeba histolytica trophozoites [33].

*Cancer (skin melanomas, hepatocellular carcinomas, other tumors, tumor cells); multi-action of protective lactobacillus PB (including L. plantarum) and/or bifidobacterial cocktails in combination with prebiotics and antibiotics; under chemotherapy to alleviate adverse effects [3, 12, 36].

Comments. PB= postbiotics. Abbreviations in the literature are in parentheses.
Conclusions:
1. At the moment, a wide range of diseases, pathologies and infections have been characterized, for which the effect of PB has been described.
2. PB acts as protective factors along metabolic axes. The concept of metabolic axial coupled effect of intestinal PB on other organs and tissues of the body has been further developed.
3. The prospects of the development and application of PB directed against groups of primary and/or secondary diseases and pathologies are noted.
4. The directions and trends of modern PB research (related to medical biotechnology and including the design of PB with access to vaccination issues) are formulated, determining the immediate prospects.
5. PB are promising directly and/or indirectly, affecting the factors of reversibility of diseases and pathologies, the ingredients of preventive and therapeutic mixtures, including components of functional nutrition (including in formulas of therapeutic and baby food).
6. The prospects of preventive and therapeutic PB recognizing GC are emphasized as a new class of physiologically active agents of a varying assembly organization that co-function with the body systems on a large scale and in a network.
7. PB based on GC and GC-type prebiotics are promising, PB as combined synergistic combinations of effectors of fundamentally different nature and with different mechanisms of action.
8. The development of synthetic synergistic and mutually stabilizing sets of PB with known structure and network multi-action (including identified primary dominant/initiating site of action in the nodes of the communication network of cascade reactions built by the experimenter) is promising.
9. The network participation of PB in the work of the interactome of the organism in accordance with the metabolic axes “Intestine—Not intestine” presupposes the mutual influence of terminal points in the axes in the forward and opposite directions, that is, regulatory connections of non-intestinal organs (including the brain) and tissues should take place on the microecological status of intestinal PB sets and its departments, which can be considered as a new factor of modulation of the general health of individuals, patients and the population.
10. There is a single probiotic compartment in the body, which functions as a network with two-way metabolic axes.

Literature


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