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FROM TRADITIONAL FERMENTED BEVERAGE TO EVIDENCE-BASED IMMUNOMODULATOR: PHARMACOLOGICAL CHARACTERIZATION OF BACTERIAL-YEAST MILK NUCLEOTIDES IN SECONDARY IMMUNODEFICIENCY MANAGEMENT (LITERATURE REVIEW AND ORIGINAL RESEARCH)

***R. Y. Hrytsko**

Department of Infectious Diseases, Danylo Halytskyi Lviv National Medical University, Lviv, Ukraine.

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***Corresponding Author: R. Y. Hrytsko**

Department of Infectious Diseases, Danylo Halytskyi Lviv National Medical University, Lviv, Ukraine.

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ABSTRACT
Nucleotides—the structural units of nucleic acids—function not merely as metabolites but as fully-fledged pharmacologically active substances with well-characterized receptor and molecular mechanisms of action. The fermented milk bacterial-yeast beverage with high nucleic acid content combines the pharmacological activity of nucleotides with probiotic and prebiotic effects, positioning it as a unique natural immunomodulator fundamentally distinct from synthetic immunotropic agents. **Objective:** To systematically synthesize scientific evidence regarding the pharmacological status of dietary nucleotides—including mechanisms of action, classification, pharmacodynamics, and position within the immunotropic agent framework—and to consolidate clinical data on the efficacy of the bacterial-yeast beverage in secondary immunodeficiency states and related pathological conditions. **Methods:** Narrative literature review (PubMed/MEDLINE, Scopus, WoS, 2000–2025) combined with the author's own clinical and laboratory investigations (1993–2016). **Results:** Nucleotides from the bacterial-yeast beverage exert pharmacological activity through: (1) TLR9 agonism (CpG-DNA → MyD88 → NF-κB → Type I IFN, IL-12); (2) salvage pathway utilization—supporting lymphocyte and enterocyte proliferation; (3) purinergic signaling (adenosine → A_2A receptors → cAMP → immunoregulation); and (4) Nod-like receptor (NLR) activation. Clinically: post-vaccination immunity enhancement by 15–22%, $CD4^+/CD8^+$ ratio and phagocytic index correction, and sIgA normalization. Unlike pharmaceutical immunotropic agents, the beverage's nucleotides act synphysiologically—through the same receptor systems activated during natural immune responses. **Conclusion:** The fermented milk bacterial-yeast beverage represents a pharmacologically substantiated, multi-target natural immunomodulator. Its advantages over synthetic immunotropic agents include: pleiotropic pharmacodynamics, physiological route of administration, absence of receptor saturation, probiotic and microbiome-normalizing effects, and population-level accessibility. Its inclusion in clinical nutrition standards for secondary immunodeficiency states is warranted.

KEYWORDS: nucleotides, pharmacologically active substances, TLR9, purinergic signaling, fermented milk beverage, kefir, immunomodulation, secondary immunodeficiency, probiotics, functional nutrition.

INTRODUCTION

The problem of secondary immunodeficiency states (SIS) is assuming increasing clinical and public health significance. Widespread antibiotic use, immunosuppressive therapy, chronic stress, nutritional deficiencies, and adverse environmental factors continuously expand the population of individuals with impaired immune competence. Secondary immunodeficiencies—a heterogeneous group of conditions characterized by reduced functional activity of cellular, humoral, or nonspecific defense mechanisms in the absence of primary genetic defects—manifest clinically as recurrent infections, suboptimal post-vaccination responses, and chronic inflammation.[1, 2]

The search for effective immunocorrection methods has traditionally focused either on pharmacological immunotropic agents (thymic peptides, synthetic enhancers, cytokines, bacterial lysates) or on nutritional support framed as nonspecific "health promotion." A third pathway—the application of food products with demonstrated pharmacologically active components—has remained undervalued despite a substantial scientific evidence base. Among such components, nucleotides and nucleic acids produced by bacterial-yeast microorganisms during milk fermentation occupy a special position.[3, 4]

This review systematically presents, for the first time, nucleotides from the bacterial-yeast beverage as pharmacologically active substances with classified mechanisms of action, specific molecular targets, and demonstrated clinical effects—establishing the scientific foundation for their inclusion among evidence-based immunomodulatory agents.

Dietary nucleic acids undergo sequential hydrolysis in the intestinal lumen: pancreatic RNase and DNase cleave polymeric nucleic acids to oligonucleotides; 5'-nucleotidases yield mononucleotides; nucleosidases produce nucleosides and nitrogenous bases, which are absorbed by enterocytes via CNT and ENT family transporters.[5,6] Systemic bioavailability of dietary purine nucleosides ranges from 40–70%, and pyrimidine nucleosides from 20–40%.[7]

Following absorption, nucleotides partition between two pathways: *de novo* synthesis (resource-intensive—up to 6 ATP per nucleotide) and the salvage pathway, which recovers nucleosides and bases from plasma. Tissues with high cellular turnover—lymphoid organs, intestinal epithelium, and bone marrow—predominantly depend on the salvage pathway, creating a window of pharmacological sensitivity to exogenous nucleotides.[8]

Dietary nucleotide deficiency significantly reduces proliferative responses of T-helper cells ($CD4^+$) to mitogens and specific antigens; nucleotide restoration normalizes these responses. Nucleotide support enhances lymphocyte IL-2 secretion, augmenting clonal T-cell expansion.[9, 10] NK cell cytotoxicity and $CD8^+$ effector activity also depend on nucleotide supply.[11]

Dietary nucleotides are associated with elevated serum IgG and IgM concentrations, improved antigen-specific antibody titers following vaccination, and higher secretory IgA content in the intestine and saliva.[12, 13] sIgA constitutes the first line of adaptive mucosal defense; its deficiency is a predictor of recurrent intestinal and respiratory infections.

Macrophages from nucleotide-supplemented animals exhibit increased phagocytic index, enhanced oxidative burst, and accelerated bacterial clearance. Unmethylated CpG motifs in bacterial DNA activate TLR9, triggering the MyD88 cascade and production of Type I IFN and IL-12.[14]

Nucleotides accelerate mitosis in intestinal crypts, increase villus height (V/C ratio), strengthen tight junctions, and reduce bacterial translocation. Nucleotide deficiency is associated with villous atrophy and increased intestinal permeability.[15]

This section is conceptually pivotal for redefining the status of the bacterial-yeast beverage—from a "beneficial food product" to a "natural pharmacological agent with identified molecular targets and classified pharmacodynamics."

From the perspective of modern pharmacology, nucleotides released from the bacterial-yeast beverage in the human body can be classified according to receptor target type and pharmacological effect:
Unmethylated CpG dinucleotide sequences in bacterial DNA are natural ligands for TLR9—an endosomal receptor that recognizes bacterial nucleic acids as PAMPs (pathogen-associated molecular patterns). CpG TLR9 agonists constitute an independent pharmacological class; their synthetic analogs (CPG 7909, MGN-1703) are undergoing clinical trials as vaccine adjuvants and antitumor immunostimulants.[16] The principal advantage of the beverage's natural CpG motifs: they are embedded in a physiological dietary context and do not elicit the excessive systemic cytokine activation characteristic of synthetic agonists.

Nucleosides absorbed from the intestine act as metabolic prodrugs: following phosphorylation by nucleoside kinases, they are converted to active nucleotides directly within lymphocytes and enterocytes. This parallels the mechanism of action of antiviral nucleoside analogs (acyclovir, tenofovir), but in a physiological rather than xenobiotic context.[8]

Adenosine and ATP, released upon nucleotide hydrolysis, are ligands for purinergic P1 (A_1, A_2A, A_2B, A_3) and P2 ($P2X_{1–7}$, $P2Y_{1–14}$) receptors. A_2A receptors are key regulators of immunological tolerance: adenosine-mediated A_2A agonism elevates intracellular cAMP in T

cells and dendritic cells, limiting excessive inflammatory responses.[17] $P2X_7$ receptors are activated by extracellular ATP and trigger the NLRP3 inflammasome, enhancing IL-1β and IL-18 processing.[18] This purinergic signaling represents a molecular mechanism previously undescribed for nucleotide dietary supplements and food products.

Certain nucleotide derivatives (di-AMP, c-di-GMP) are ligands for STING (stimulator of interferon genes) and NOD1/NOD2 receptors—components of cytoplasmic innate immune surveillance. STING activation induces Type I interferons independently of the TLR pathway and is the subject of active oncoimmunological research.[19]

Nicotinamide (NMN, NAD^+) and flavin (FAD) nucleotides are indispensable coenzymes for redox reactions. Adequate supply of their precursors (adenosine, nicotinamide) supports antioxidant capacity and mitochondrial function in immune cells.[20]

Key pharmacodynamic distinctions between the natural nucleotides of the bacterial-yeast beverage and synthetic immunotropic agents are presented below. Synthetic immunotropic agents (thymic peptides, polyoxidonium, recombinant interferons) act predominantly on one or two molecular targets—this constitutes both their strength (potency at that target) and their weakness (absence of physiological balancing among immune effectors). The beverage's nucleotides, conversely, act *synphysiologically*: they engage the same receptor systems (TLR9, purinergic receptors, STING, salvage kinases) that are activated during normal immune responses to infection. This ensures automatic balancing between pro-immune and regulatory signals—a phenomenon that virtually precludes autoimmune hyperactivation, a risk associated with synthetic immunotropic agents.[21]

Specific pharmacodynamic advantages of the beverage's nucleotides include: **Absence of receptor saturation:** Unlike recombinant cytokines (IFN, G-CSF) that desensitize receptors with prolonged use, nucleotides act through metabolic pathways with upregulation that does not diminish upon repeated administration.[4] **Organ-specific distribution:** Nucleotides preferentially accumulate in tissues with the highest cellular turnover (GALT, bone marrow, intestinal epithelium)—precisely those where immune competence is most frequently compromised in SIS.[8] **Synergy with vaccines:** TLR9 agonists are among the most potent natural vaccine adjuvants—they enhance antigen presentation by dendritic cells and accelerate B-cell memory formation. Beverage administration during vaccination represents a substantiated strategy for enhancing immunogenicity.[22] **Enteral-systemic pharmacokinetic profile:** Oral administration with gradual absorption provides sustained plasma levels of nucleotide precursors over 6–8 hours, avoiding "peaks" and the associated risk of excessive cytokine response characteristic of parenteral cytokine administration.[23]

According to the pharmacological classification of immunotropic agents (WHO/ATC system, group L03—"Immunostimulants"), nucleotides from the bacterial-yeast beverage can be qualified as: **1. Natural Mucosal Immunostimulants** (analogous to L03AX—"Other cytokines and immunomodulators"). This group includes bacterial lysates (Broncho-Vaxom, OM-85), ribomunyl, and now—bacterial nucleic acids. The principal distinction from bacterial lysates: the beverage contains live probiotic microorganisms and structurally intact nucleic acids, rather than heat-inactivated fragments. **2. Nutritional Immunomodulators**—a class formally recognized in clinical nutritiology. ESPEN (European Society for Clinical Nutrition) recommends nucleotide-containing enteral nutrition in critical illness, surgical interventions, and chemotherapy.[24] The bacterial-yeast beverage conforms to this profile. **3. Natural Origin TLR Adjuvants**—a distinct functional class for regulatory purposes (vaccine adjuvants). The beverage's nucleotides represent the first example of a food-derived TLR9 adjuvant that can be administered orally at physiological concentrations.

Commercially available synthetic nucleotide preparations (Sodium Nucleinate, Polyoxidonium as a polymeric derivative) and registered CpG-oligonucleotide-based adjuvants exist. Compared to these, the natural bacterial-yeast beverage possesses fundamental pharmacological advantages:
Synthetic CpG oligonucleotides consist of identical sequences in large quantities that may elicit excessive systemic inflammatory responses. The beverage's bacterial DNA contains diverse CpG sequences distributed in a chromatin context and released gradually—reproducing the natural picture of bacterial infection, to which the immune system responds with a calibrated response.[14]

Synergism of nucleotides and probiotics: The beverage's nucleotides are delivered together with live probiotic bacteria that simultaneously activate TLR2 (via lactobacterial lipoteichoic acid) and TLR4 (via yeast LPS). This multi-receptor activation provides broader coverage of innate immune components than mono-agonists alone.[25]

No requirement for injection: All registered TLR agonists are administered parenterally or locally. The beverage's nucleotides represent the only natural TLR9-activating substrate with clinically confirmed oral activity in humans.[22]

Duration and safety of use: Synthetic immunotropic agents are typically prescribed in 2–4 week courses due to risks of receptor desensitization or adverse effects. The bacterial-yeast beverage as a food product is suitable for long-term (months to years) continuous use without

restrictions, corroborated by the experience of populations traditionally consuming kefir and kumiss.[26]

GALT (gut-associated lymphoid tissue) constitutes approximately 70% of the total immune cell mass and maintains continuous dialogue with luminal microbiota through PRRs (pattern recognition receptors). Microbiome composition determines the basal tone of systemic immunity: dysbiosis is associated with increased intestinal permeability, bacterial product translocation, systemic inflammation, and SIS.[27, 28]

Unlike single-strain probiotic preparations, the bacterial-yeast beverage delivers a symbiotic consortium—*Lactobacillus* spp., *Lactococcus* spp., *Leuconostoc* spp., and *Saccharomyces*/ *Kluyveromyces*—with demonstrated synergistic action. Lactobacilli produce lactic acid and bacteriocins, lowering pH and inhibiting pathogens; yeast mannan oligosaccharides serve as prebiotics for *Bifidobacterium* spp. Systematic reviews indicate that kefir-like beverages modulate the relative abundance of *Bifidobacterium*, *Blautia*, and *Faecalibacterium*—species with established immunoregulatory activity.[29]

Fermentation of the beverage's prebiotic components by the colonic microbiome generates butyrate, propionate, and acetate. Butyrate inhibits histone deacetylases (HDACs), epigenetically activating *Foxp3* genes in T-cell precursors, leading to regulatory T-cell (Treg) differentiation. This Treg-inducing effect represents a unique link between nutrition, microbiome, and systemic immunological homeostasis.[30]

The concept of the microbiome as a "second pharmacological organ"—a community of microorganisms producing pharmacologically active compounds (SCFAs, neurotransmitters, vitamins, nucleotides)—is gaining recognition in clinical pharmacology.[31] The bacterial-yeast beverage, by restoring eubiosis, thereby restores the "second pharmacological organ"—the microbiome's productive capacity for immunoregulatory metabolites. This represents a qualitatively new level of pharmacological action, unattainable by any known synthetic immunotropic agent.

Kumiss and kefir possess millennia-old traditions of medical use, previously attributed vaguely to "general strengthening effects." Modern molecular pharmacology provides specific explanations: over 200 biologically active components have been identified in kumiss and kefir, among which nucleotides and nucleic acids are pharmacologically most significant.[32, 33]

The author's own analytical data confirm that the bacterial-yeast beverage from cow's milk, produced according to an optimized technological protocol, contains nucleic acids at concentrations of 0.8–1.5 mg/mL (spectrophotometrically at 260 nm), with CpG motif and nucleoside composition corresponding to effective immunostimulatory concentrations validated in clinical studies of synthetic analogs.[34] At a daily consumption of 200–300 mL of beverage, the patient receives 160–450 mg of nucleotide precursors—a dose 3–5 times higher than the average daily alimentary nucleotide intake from conventional nutrition.

CLINICAL EFFICACY IN SECONDARY IMMUNODEFICIENCY

SIS are classified according to the predominantly affected compartment: combined (cellular + humoral), predominantly T-cell, predominantly B-cell, phagocytosis defect, complement defect. Each compartment correlates with specific clinical manifestations and specific pharmacological targets of nucleotides.[1, 2]

The author's investigations, conducted from 1994 to 2001 in outpatient clinics and infectious disease hospitals of Lviv, included patients with SIS receiving diphtheria toxoid-containing vaccines. Regimen: bacterial-yeast beverage 200 mL/day starting 14 days before vaccination and continuing for 21 days post-vaccination. Results: specific anti-diphtheria IgG at day 30 post-vaccination were 15–22% higher in the study group; seroprotection rate (IgG ≥0.1 IU/mL)—15–22 percentage points higher; seroprotection duration—prolonged by 2–3 months.[35, 36] Mechanism: TLR9-mediated dendritic cell activation enhances antigen presentation and accelerates B-cell affinity maturation.

The author's clinical series (Infectious Diseases Department of LNMU, 1998–2013) documented $CD4^+/CD8^+$ correction (from 0.9±0.2 to 1.4±0.3, $p<0.05$), neutrophil phagocytic index increase of 38%, and salivary sIgA normalization in patients with chronic hepatitis and recurrent respiratory infections during a three-month beverage course.[37] The gradual nature of the effect (peak at 4–6 weeks) corresponds to the pharmacokinetics of nucleotide saturation of lymphocytes via the salvage pathway.

Kefir-like beverages have demonstrated improved glycemic parameters and lipid profiles in randomized studies of type 2 diabetes mellitus.[38] Butyrate-mediated HDAC inhibition in colonocytes exerts antiproliferative effects on colorectal cancer cells.[39] In gerontological terms, probiotic-nucleotide correction partially restores microbiome diversity and NK-cell activity in elderly individuals.[40]

COMPARATIVE ANALYSIS: MULTI-TARGET VS. MONO-TARGET AGENTS

Synthetic immunotropic agents—thymic peptides (Thymalin, Tactivin), polymeric immunostimulants (Polyoxidonium), recombinant cytokines (IFN-α, G-CSF), bacterial lysates (Broncho-Vaxom)—are agents with known mechanisms of action, but each acts on a limited number of targets. The bacterial-yeast beverage is

a multi-target pharmacological agent of natural origin that simultaneously:
Activates TLR9 (CpG-DNA) → IFN-I, IL-12 → Th1, NK, CTL
Activates TLR2 (lactobacillary lipoteichoic acid) → NF-κB → monocytes/macrophages
Supports salvage pathway → T- and B-lymphocytes, enterocytes
Induces purinergic signaling (A_2A → cAMP → Treg balancing)
Modulates microbiome → SCFAs → Treg, IL-10, intestinal barrier
Normalizes GALT → sIgA → mucosal protection

No registered synthetic immunotropic agent simultaneously encompasses all these levels. Moreover, the beverage's safety profile is incomparably superior: contraindications are limited to lactose and casein intolerance; cost is incomparable to pharmaceutical preparations; accessibility—without prescription. These characteristics define the beverage's niche: long-term (months to years), continuous, non-toxic, population-accessible immunocorrection—what no synthetic immunotropic agent can offer.

CONCLUSIONS AND RECOMMENDATIONS

Nucleotides from the bacterial-yeast beverage constitute fully-fledged pharmacologically active substances with identified molecular targets (TLR9, purinergic P1/P2 receptors, STING, NLR, salvage kinases), specific pharmacodynamic mechanisms, and reproducible clinical effects. They should be qualified as natural multi-target mucosal-type immunomodulators—a distinct pharmacological class within nutritional immunomodulators.

CpG motifs in the beverage's bacterial DNA are natural TLR9 agonists—the same class of molecules that, in synthetic form (CPG 7909, MGN-1703), are undergoing clinical trials as vaccine adjuvants and antitumor immunostimulants. The natural delivery format (food matrix, oral, at physiological concentrations) eliminates risks associated with synthetic analogs.

Purinergic signaling (adenosine A_2A receptors, ATP $P2X_7$ receptors) represents a previously undescribed pharmacological mechanism for fermented milk beverages and opens new research perspectives.

The concept of the microbiome as a "second pharmacological organ" provides the bacterial-yeast beverage with an additional pharmacological dimension: restoration of eubiosis restores endogenous production of immunoregulatory metabolites (SCFAs, neurotransmitters)—an effect fundamentally unattainable by any synthetic agent.

The author's own investigations (1993–2013) confirm the clinical efficacy of the bacterial-yeast beverage in SIS: post-vaccination immunity enhancement by 15–22%, normalization of $CD4^+/CD8^+$ ratio and phagocytic index, and increased sIgA.

Compared to standard synthetic immunotropic agents, the bacterial-yeast beverage offers advantages in: breadth of pharmacodynamic coverage (multi-targeting), safety profile, duration of use, absence of receptor desensitization, and cost accessibility.

Recommendations

Initiate a randomized controlled clinical trial (RCT) of the bacterial-yeast beverage in SIS with assessment of TLR9-mediated markers (IFN-α, IL-12) and purinergic parameters (lymphocyte cAMP) as primary endpoints—to confirm pharmacological mechanisms in humans.

Develop a standard for nucleic acid content in bacterial-yeast beverages (minimum effective concentration—no less than 0.8 mg/mL) as a quality criterion for pharmacologically active products and promote its inclusion in relevant national standards.

Include the bacterial-yeast beverage with confirmed nucleic acid content in clinical protocols for nutritional support in SIS (including chemotherapy-associated immunodeficiency, post-COVID syndrome, geriatrics)—in accordance with ESPEN recommendations for nucleotide-containing enteral nutrition.

Submit a proposal to the Ministry of Health of Ukraine for inclusion of the immunomodulatory bacterial-yeast beverage in the list of traditional medicine/nutrient therapy agents with proven efficacy—with clear pharmacological justification distinguishing it from over-the-counter immunotropic agents of undefined action.

Conduct pharmacogenomic studies to identify polymorphisms in *TLR9* (rs352140, rs5743836), *ADORA2A* (A_2A receptor), and *NOD2* that may determine individual sensitivity to nucleotide immunocorrection—for development of personalized beverage administration regimens.

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