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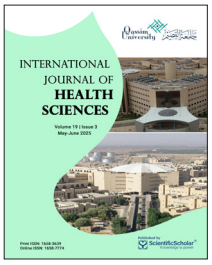

Editorial

Lactobacillus reuteri paradigm - How loss of a sentinel of gut-brain-metabolic health fuels modern epidemics and era of microbial restoration

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Since its early characterization in the late 1980s, *Lactobacillus reuteri,* also classified as *Limosilactobacillus reuteri* (*L. reuteri*), has emerged as a significant microbe in the realm of probiotics.[1] This Gram-positive, rod-shaped, facultative anaerobic bacterium was once viewed to be only a commensal inhabitant of the gastrointestinal (GI) tract but is now recognized as a vital modulator of health and disease.[2] The extensive scientific literature published till date attests to its diverse and constantly evolving therapeutic promise not only just in GI health but also in immune regulation, neurobiology, cancer therapeutics, and even systemic disease prevention. This editorial provides a comprehensive review of key findings over the decades, highlighting the transformative journey of *L. reuteri* from normal commensal to a guardian of holistic health.

The foundational years of *L. reuteri* research focused primarily on its taxonomy, colonization capabilities, and natural existence in the human and animal gut.[3] By the mid-1990s, early trials began to highlight its probiotic effects in maintaining GI homeostasis.[4-6] A series of pivotal studies in the late 1990s and early 2000s demonstrated that *L. reuteri* could outcompete pathogenic bacteria by producing antimicrobial compounds such as reuterin, a broad-spectrum antimicrobial agent, which selectively inhibits pathogens while preserving beneficial microbes.[1,7-9]

The earliest and most known clinical uses of *L. reuteri* were for treating infantile colic. A number of randomized controlled trials found that supplementation with *L. reuteri* DSM 17938 resulted in a substantial decrease in crying time among colicky breastfed infants compared to placebo groups.[10] This research paved the way for subsequent pediatric treatments, including diarrhea, constipation, and functional GI disorders.[11,12] In children and adults, *L. reuteri* has been found to enhance gut motility, restore microbial balance, and improve stool consistency, making it an important tool for treating both acute and chronic GI complaints.[11]

L. reuteri has been extensively researched as an adjunctive therapy for *Helicobacter pylori* (*H. pylori*) eradication.[13-15] A meta-analysis published in 2024 with findings from eight randomized controlled trials spanning 1,000 patients revealed that *L. reuteri* supplementation significantly improved *H. pylori* eradication rates when added to conventional triple therapy.[16] The study also proposed additional benefits, such as a reduction in GI side effects such as nausea, diarrhea, and bloating.[16] Hence, *L. reuteri* not only supports the gut microbiome during antibiotic

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use but may also directly impair *H. pylori* colonization and survival.

L. reuteri plays a plausible therapeutic role in inflammatory bowel diseases (IBDs), such as Crohn's disease and ulcerative colitis.[4,17,18] Experimental models demonstrated *L. reuteri* to reinforce the intestinal barrier, block pro-inflammatory cytokine production (e.g., tumor necrosis factor-alpha, interleukin (IL)-6), and promote the expansion of regulatory T-cells.[19-21] These immunomodulatory properties position *L. reuteri* as a promising adjunct therapy in reducing the inflammatory burden in IBD. Although further large-scale human trials are warranted, the pre-clinical evidence highlights the immunological sophistication of this microorganism.

However, an escalating concern in recent years is that the modern human population, particularly in industrialized nations, is increasingly deficient in naturally occurring *L. reuteri*.[22] Comparative analyses of gut microbiota across diverse populations have revealed that *L. reuteri*, once a common component of the human gut ecosystem, is now typically gone from the microbiomes of most Western people.[23] One of the landmark researchers attributed this loss to multiple factors linked to lifestyle and environmental alterations, including consumption of ultra-processed food in overly sanitized environments, increased rates of cesarean sections, formula feeding, and, most notably, the rampant and indiscriminate use of broad-spectrum antibiotics. Collectively, these factors contribute to the disruption of microbial colonization and hinder vertical transmission of beneficial strains such as *L. reuteri* from mother to newborn, resulting in its near extinction in many individuals today.[24]

The clinical implications of this microbial depletion are profound. The absence of *L. reuteri* has been associated with increased susceptibility to immune dysregulation, inflammatory disorders, allergic diseases, metabolic syndrome, and even behavioral abnormalities.[25] Unlike pathogens, which are eliminated to improve health, the disappearance of beneficial microorganisms such as *L. reuteri* is likely to impair mucosal immunity, decrease microbial diversity, and raise the risk of dysbiosis, a known contributor to conditions ranging from asthma to anxiety.[19,26] The depletion of *L. reuteri* is also associated with diminished gut barrier, digestive disturbances, and weakened immunity. Clinical studies demonstrate that reintroducing *L. reuteri* can enhance mucosal immunity, reduce low-grade systemic inflammation, and improve metabolic parameters such as insulin sensitivity and lipid metabolism. Mechanistically, *L. reuteri* exerts these effects through aryl hydrocarbon receptor (AhR) and modulates IL-10, transforming growth factor beta and T-regulatory cell populations, highlighting its critical role in immune resilience.[19,27]

The therapeutic leverage of *L. reuteri* has expanded from the gut to the gut-brain axis, a bidirectional communication network linking the enteric nervous system to the central nervous system through neural, immune, and hormonal channels. Experimental evidence indicates that this probiotic strain modulates vagus nerve activity, stimulating the release of key neurochemicals such as gamma-aminobutyric acid (GABA) and oxytocin. Interestingly, a positive response in social behavior in autism spectrum disorder models has been observed.[28] Particularly noteworthy are findings showing improved social interaction patterns in pre-clinical models of autism spectrum disorder following *L. reuteri* administration.

Cutting-edge research from 2022 onward highlights the remarkable neuroprotective potential of *L. reuteri* against radiation-induced brain injury. A preclinical study demonstrated that oral administration of *L. reuteri* ameliorated cognitive dysfunction in irradiated mice. The observed neuroprotection appears to be mediated through a triad mechanism: Remodeling of gut microbial ecology, attenuation of systemic inflammatory markers, and normalization of brain-derived neurotrophic factor levels. These findings put *L. reuteri* as a novel therapeutic candidate for neuroinflammatory and neurodegenerative pathologies, potentially revolutionizing probiotic application in neurological medicine.[29]

Another fascinating aspect in *L. reuteri* research covers oncology, particularly colorectal cancer (CRC).[22] Increasing evidence points to gut dysbiosis as a contributing factor in CRC pathogenesis. *L. reuteri* produces reuterin and histamine, both of which have shown anti-inflammatory and anti-tumorigenic properties.[30] Reuterin selectively induces oxidative stress in cancer cells, leading to DNA damage and apoptosis. A pivotal study in 2023 reported that *L. reuteri* modulates gene expression in tumor cells, inhibits proliferation, and reshapes the tumor microenvironment to promote immune-mediated clearance.[31] Such evidences not only reinforces the concept of microbiota-driven tumor modulation but also introduces *L. reuteri* as a candidate for probiotic-based cancer prevention strategies.

Beyond its local GI effects, *L. reuteri* demonstrates significant systemic immunomodulatory effects. It regulates immune tolerance by promoting the differentiation of $CD4^+$ T-cells into regulatory T-cells (Tregs) populations, coupled with a shift toward anti-inflammatory cytokine profiles.[30] Moreover, its metabolic byproducts, including indole derivatives and short-chain fatty acids mediate additional immune-regulatory effects through interaction with AhRs and G-protein-coupled receptors.[19,30] The molecular interactions coordinate immune homeostasis across mucosal barriers and systemic compartments, proposing promising clinical applications in autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, and type 1 diabetes.

Clinical studies demonstrate that *L. reuteri* is effective in managing urogenital infections, including bacterial vaginosis.

It can successfully colonize the vaginal epithelium, where it acidifies the microenvironment and inhibits pathogens such as *Gardnerella vaginalis* and *Candida albicans*.[32] Emerging research indicates that this microbial strain may influence endocrine regulation through indirect effects on estrogen metabolism.[33] These observations significantly expand the therapeutic scope of *L. reuteri* from gut and systemic health to reproductive and hormonal health.

L. reuteri has demonstrated significant promise in oral health. Clinical studies have shown that chewing gums or lozenges containing *L. reuteri* can reduce gingivitis, periodontitis, and plaque formation by inhibiting pathogens such as *Porphyromonas gingivalis*. By adhering to oral surfaces and reducing inflammation, it presents a novel non-drug approach for periodontal disease and dental caries.[34]

Despite the status of *L. reuteri* as a leading probiotic over the past four decades, it is essential to recognize that the benefits of *L. reuteri* are strain-specific. Key strains DSM 17938, ATCC PTA 6475, and ATCC 55730 show distinct differences in tissue colonization, bioactive metabolite production, and immune system modulation.[4] Thus effective probiotic interventions therefore require careful strain selection, optimal dosing, and treatment duration to achieve targeted clinical outcomes.

L. reuteri has evolved from a gut-dwelling commensal to a pivotal regulator of whole-body health. With demonstrated benefits in gastroenterology, immunology, neurology, oncology, and women's health, this versatile probiotic exemplifies the potential of precision microbiome medicine. By stimulating targeted microbial communities, metabolic pathways, immune function, and neural signaling, *L. reuteri* represents a major advancement in probiotic therapeutics. Yet, the increasing disappearance of *L. reuteri* in modern human microbiomes raises an urgent public health concern. Reintroducing and restoring this key organism through supplementation, diet, or microbiota transplants could represent a foundational step toward combating the epidemic of chronic, inflammatory, and neuropsychiatric diseases seen in today's population. The era of personalized, microbiome-informed medicine may well have its roots in the probiotic promise of this remarkable microorganism.

The microbial loss is not a benign transition; it has coincided with a significant increase in chronic and inflammatory disorders throughout the world. According to emerging research, the decline of *L. reuteri*, known for its powerful immune-regulating, anti-inflammatory, and neuroprotective properties, may be contributing to the current epidemic of allergies, autoimmune diseases, metabolic syndrome, irritable bowel syndrome, neurodevelopmental disorders, and even certain cancers. Thus, the disappearance of *L. reuteri* from the human microbiome might be both a consequence of contemporary life and a hidden cause of present-day global health challenges.

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