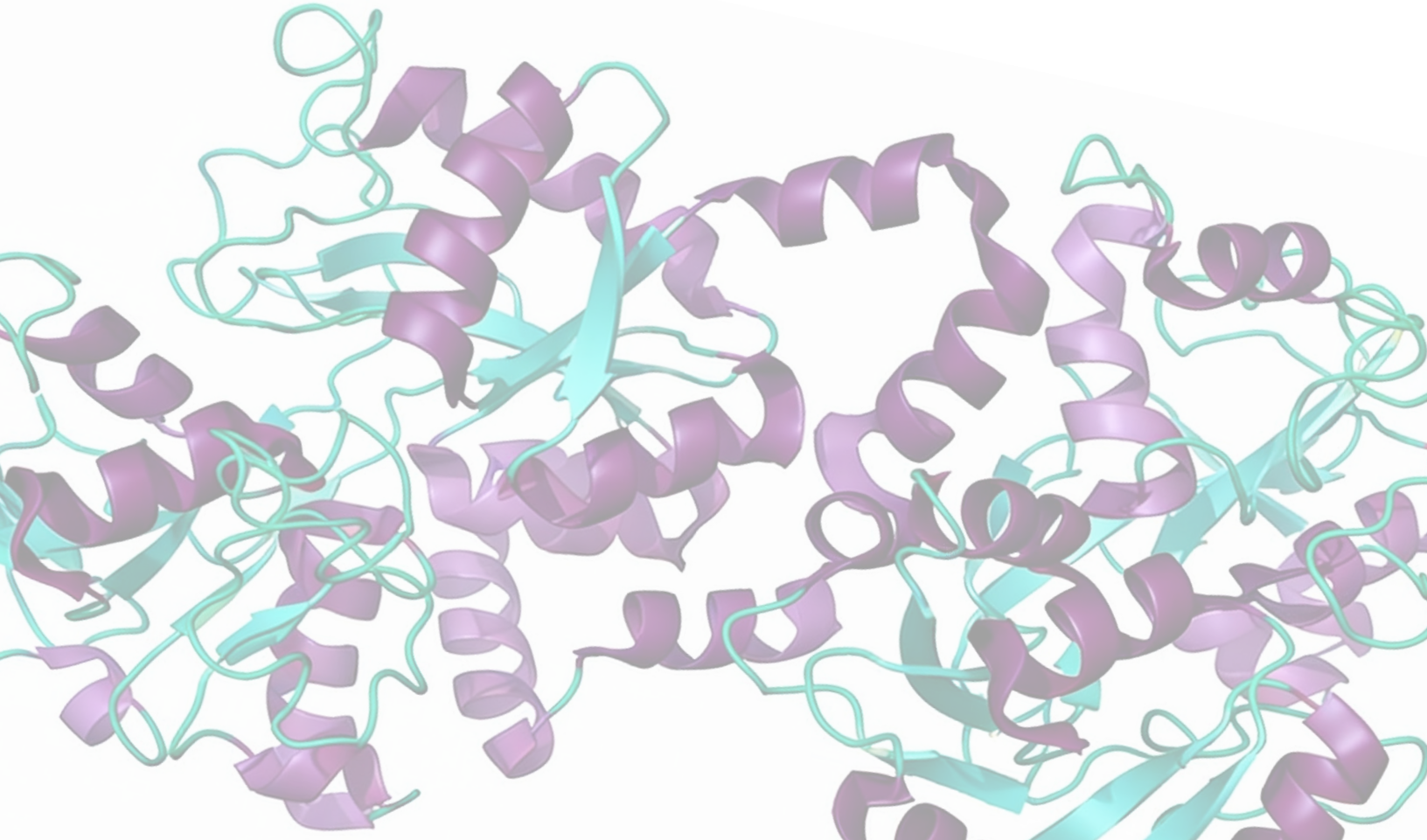

effera®'s Role in Microbiome, Barrier & Gut Resilience

Human-identical lactoferrin supports gut health through selective microbiome modulation, epithelial barrier integrity, and immune-inflammatory balance.

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Executive Summary

Gut health is dependent on the coordinated interaction between the microbiome, intestinal barrier integrity, immune signaling, and nutrient regulation. Disruptions in these systems, including microbial imbalance, impaired barrier function, oxidative stress, inflammation, and altered iron homeostasis, can negatively impact gastrointestinal and systemic health.

effera® Human Lactoferrin is the first commercially available human-identical lactoferrin produced through precision fermentation. Structurally and functionally equivalent to native human lactoferrin, effera® Human Lactoferrin supports gastrointestinal health through multiple complementary biological mechanisms:

- Microbiome support by selectively promoting beneficial bacteria while limiting undesirable microbial overgrowth
- Gut barrier support through enhancement of epithelial lining integrity and maintenance of healthy intestinal permeability
- Immune and inflammatory balance through modulation of oxidative stress, inflammatory signaling, and iron availability

Rather than acting through a single pathway, lactoferrin works within the body's existing regulatory systems to support microbiome balance, epithelial integrity, immune function, and gastrointestinal resilience at the molecular, cellular, and tissue levels.

The "Scientific Why": Understanding Lactoferrin

Lactoferrin is a bioactive iron-binding protein that is naturally present throughout the gastrointestinal tract and on mucosal surfaces, where it plays a central role in supporting gut health and gastrointestinal homeostasis. Produced by epithelial cells and secreted onto mucosal surfaces, lactoferrin helps protect the intestinal barrier, regulate iron availability, and support communication between the microbiome and mucosal immune system. Its ability to bind iron, interact with microbial structures, and modulate inflammatory signaling, lactoferrin helps support a balanced and resilient gastrointestinal system.

effera® Human Lactoferrin Overview:

Historically, supplemental lactoferrin was limited to bovine sources (bLF). **effera®** is the first human-equivalent lactoferrin produced via precision fermentation. It is **structurally identical** to the protein found in the human body, sharing the same amino acid sequence. effera® exhibits comparable digestive stability and degradation profiles to hLF, with both proteins being digested at similar rates during gastric and intestinal transit making it superior to bovine.[2] *Unlike cow lactoferrin,* effera® is human-identical - matching the structure and function of native human lactoferrin - allowing it to work seamlessly within the body's regulatory systems. This ensures:

1. **High Bioavailability:**
   Retains a higher proportion of intact protein during gastric transit compared to bovine alternatives.
2. **Targeted Function:**
   Mirrors the biological signaling and iron-binding affinity of natural human lactoferrin.
3. **Human Recognition:**
   Identified by the body as native, supporting natural physiological function and compatibility.

Produced by epithelial cells and secreted onto mucosal surfaces, lactoferrin helps protect the body's barriers and regulate iron balance.

Microbiome Modulation

The gut microbiome is a complex and dynamic ecosystem composed of microorganisms that play a central role in maintaining gastrointestinal homeostasis, immune function, and overall health and mood.[3] A balanced microbiome is essential for maintaining immune system function, supporting nutrient metabolism, and protecting against pathogenic invasion, thereby contributing to optimal gastrointestinal functioning.[3]

Lactoferrin (LF) has been shown to modulate the gut microbiome through multiple complementary mechanisms, functioning - in part - as a prebiotic compound. LF exerts selective pressure within the microbial environment by promoting the growth of beneficial bacteria while inhibiting pathogenic species.[4] This selective activity is a key feature distinguishing LF from traditional prebiotics, as it directly supports microbial balance rather than indiscriminate fermentation. Emerging evidence also suggests that LF-derived glycans contribute to these prebiotic effects. Vega-Bautista et al.[5] reported that N-glycans derived from LF may stimulate the expression and translation of proteins involved in carbohydrate transport into the bifid shunt pathway, thereby supporting the metabolic activity and growth of bifidobacteria (beneficial bacteria).[5] In addition, digestion of LF can generate bioactive peptides with antimicrobial and bifidogenic properties, further shaping the microbial environment.[6,7]

In vitro studies demonstrate that LF can directly promote the growth of specific probiotic strains, including *Lactobacillus acidophilus, L. plantarum,* and *Pediococcus acidilactici*.[5] Mechanistically, certain probiotic strains, including L. acidophilus, B. breve, B. bifidum, and B. infantis, express LF-binding proteins on their membranes, allowing LF to bind and selectively support their growth and persistence within the gut ecosystem.[4] Moreover, these strains appear to be well adapted to low-iron environments,[8] created by LF iron-binding activity. These effects appear to be dose-dependent, as higher concentrations of LF may exert inhibitory effects on microbial growth due to its iron-binding capacity.[5] LF also contributes to microbial defense by decreasing epithelial cell monolayer permeability, thereby limiting pathogen translocation, and supporting a more controlled intestinal environment.[4] Additionally, LF may exert enhanced prebiotic effects when combined with other bioactive compounds, further promoting the proliferation of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* spp.[6]

Studies have demonstrated increased microbial populations in both the small and large intestines following supplementation with LF in combination with probiotics.[9] These effects are thought to be partially mediated by LF's iron-binding capacity, which influences microbial growth dynamics through regulation of iron availability. Clinical and preclinical evidence further supports these effects. In elderly women, supplementation with LF in combination with galactooligosaccharides for nine weeks resulted in increased gut microbiome diversity and elevated levels of *Bifidobacterium* and *Lactobacillus*.[10]

Peterson et al.[11] reported effera® maintained overall gut microbiome stability in healthy adults, with no significant changes in alpha- or beta-diversity, suggesting a non-disruptive, well-tolerated effect. effera® induced targeted compositional and metabolic shifts, including enrichment of beneficial, SCFA-producing genera and increased acetate production, consistent with a selective, prebiotic-like modulation of microbial function rather than broad restructuring. These effects may be partially mediated by the iron-binding properties of LF, which can create a low-iron environment that selectively favors beneficial microbial taxa adapted to these conditions.[45]

To better understand how effera® works in the gut, we evaluated it using an advanced human gut simulation platform that recreates digestion, the gut microbiome, and interactions with the intestinal lining. effera® increased the production of beneficial short-chain fatty acids (SCFAs), strengthened intestinal barrier integrity as measured by transepithelial electrical resistance (TEER), supported expression of the tight junction proteins ZO-1 and occludin, and reduced the inflammatory chemokine CXCL-10. Beneficial microbial biomass also increased in a dose-dependent manner, with enrichment of SCFA-producing bacteria beginning at 100 mg/day. Across matched doses, effera® consistently outperformed

bovine lactoferrin in supporting gut barrier integrity and beneficial microbial growth, while measurable improvements in SCFA production and inflammatory signaling were observed beginning at doses as low as 50 mg/day.

Key Takeaway:

Selectively promotes beneficial bacteria such as Bifidobacterium and Lactobacillus while limiting pathogenic overgrowth.

Provides glycans and bioactive peptides that support beneficial microbial activity and host–microbe balance.

effera® supports microbial resilience and SCFA production without broadly disrupting microbiome structure.

Gut Integrity Modulation

The integrity of the intestinal epithelial barrier is fundamental to gut health, acting as a critical line of defense that regulates the passage of nutrients while preventing the translocation of pathogens, toxins, and antigens into underlying tissues. Disruption of this barrier can lead to increased intestinal permeability and downstream inflammation, contributing to a range of gastrointestinal and systemic conditions.[13,14]

Lactoferrin (LF) has been shown to exert multifaceted effects on the intestinal epithelium, supporting both barrier integrity and epithelial function. Studies demonstrate that LF promotes the growth, differentiation, and secretory activity of intestinal epithelial cells, which are essential for maintaining mucosal structure and function.[1,13,15] Both in vitro and in vivo findings suggest that LF not only protects intestinal tissues from damage, but also actively supports their repair following injury.[15]

At the molecular level, LF influences key signaling pathways involved in inflammation and cellular homeostasis. Wu et al.15 demonstrated that iron-free lactoferrin (apo-LF) modulates the NF-κB/PPAR signaling pathway, resulting in reduced production of pro-inflammatory cytokines and protection against intestinal inflammatory injury. This anti-inflammatory activity is particularly relevant in preserving epithelial lining integrity under conditions of stress or immune activation.

In addition to its immune balancing effects, LF directly strengthens the physical structure of the gut barrier. Zhao et al.13 showed that LF enhances intestinal epithelial cell proliferation while simultaneously decreasing paracellular permeability. These effects are mediated, in part, through the upregulation of tight junction proteins, including claudin-1, occludin, and ZO-1, which are essential for maintaining epithelial cohesion and barrier function.[6,16] LF has also been shown to restore transepithelial electrical resistance and inhibit caspase-3-mediated apoptosis, further supporting epithelial integrity.[6] These mechanisms help support a stronger and more resilient intestinal barrier, promoting healthy permeability, both of which are important for normal digestive function and mucosal defense.

Beyond maintaining barrier function, LF plays a critical role in gut lining repair and regeneration. It promotes epithelial cell growth and differentiation, supports intestinal maturation (particularly in early life), and supports a healthy mucosal barrier from oxidative and inflammatory damage.[9,21] In conditions of intestinal stress, LF has been shown to support gut integrity and help maintain healthy inflammatory balance, including in sensitive populations at risk for necrotizing enterocolitis (NEC).[4,6,10] Preclinical and clinical evidence further supports the functional relevance of these mechanisms. Oral LF supplementation has been shown to enhance gut barrier integrity and improve nutrient absorption, positioning it as a promising functional alternative to colostrum. In human intestinal epithelial models, LF increases transepithelial electrical resistance and reduces permeability, while preserving tight junction morphology under inflammatory or bacterial challenge.[17,18] In vivo, LF supplementation has been associated with both structural and functional health of the gut following stress, as demonstrated in a rat short-bowel model.[17]

Key Takeaway:

Promotes epithelial growth, repair, and intestinal lining resilience.

Enhances tight junction proteins to support gut barrier integrity and permeability control.

Helps protect the gut environment under inflammatory or oxidative stress while supporting nutrient absorption.

Gut Immune and Inflammation

The link between immune health and the gut is well established. The gastrointestinal tract contains more than half of the body's lymphocytes, making it a central organ in immune function.[19,20] Interactions between microbial antigens and pattern recognition receptors (PRRs) in the intestinal epithelium drive immune responses that support homeostasis and protect against infection.[21] The gut microbiome plays a key role in modulating inflammation and maintaining barrier integrity. Microbial activity supports mucosal defense and immune signaling, while disruptions in this system can increase susceptibility to inflammation and impair epithelial function.[21,22] Disruptions in this system can impair barrier function, increase susceptibility to infection, and promote chronic inflammation.[20]

LF plays an important role in a healthy inflammatory response and maintaining immune homeostasis.

Lactoferrin's ability to bind a range of compounds, including iron and endotoxins such as lipopolysaccharide (LPS), plays a central role in regulating inflammation.[17,18] By tightly binding iron, LF helps maintain iron balance and limits the formation of reactive oxygen species (ROS) generated by excess free iron.[1,13,18,23] LF has been shown to attenuate mitochondrial ROS generation and reduce oxidative DNA damage induced by lipopolysaccharide (LPS), while also counteracting the neutrophil oxidative burst.[24,25]

Through its effects on oxidative stress, LF mitigates inflammatory signaling. Reduction in oxidative stress has been associated with decreased production of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β).[15,24] In addition, iron-free LF (apo-LF) has been shown to modulate inflammation at the epithelial level through the NF-κB/PPAR signaling pathway, a key regulator of inflammatory responses.[26]
Endogenous LF concentrations vary across the lifespan levels in colostrum support intestinal tissue

development and beneficial bacterial growth in infancy, and lower levels in mature milk helping to maintain epithelial cell function. LF supports the growth, differentiation, and secretory activity of intestinal epithelial cells, which are essential for maintaining barrier integrity.[1,13,15] Disruptions in the gut microbiota can impair barrier function and nutrient absorption, whereas LF helps support a balanced gut microbiome by encouraging the growth of beneficial bacteria such as Bifidobacterium and Lactobacillus1, which are associated with healthy digestion and a well-functioning intestinal environment.

Both preclinical and clinical evidence suggest that LF supports intestinal barrier function and integrity. LF has been shown to enhance epithelial cell growth while reducing paracellular permeability, in part through the regulation of tight junction proteins.[13] Additionally, apo-LF has been shown to balance inflammatory cytokine production and protect against intestinal inflammatory stress through modulation of NF-κB/PPAR signaling.[15] These findings suggest a role for LF in maintaining epithelial integrity under normal inflammatory conditions.

LF also plays a role in iron metabolism within the gut. Iron absorption occurs primarily in the duodenum and upper jejunum, and LF has been proposed to regulate this process through interactions with epithelial receptors. In vitro evidence suggests that LF may facilitate iron uptake by binding to membrane proteins or LF-specific receptors, with receptor expression increasing under low-iron conditions to enhance absorption.[27] Regulation of iron availability also influences microbial composition, supporting a balance between beneficial and pathogenic bacteria.[28]

Key Takeaway:

Binds free iron to reduce oxidative stress and limit inflammation-driving reactive oxygen species.

Supports healthy inflammatory signaling through cytokine and NF-κB/PPAR pathway modulation.

Reinforces gut barrier and microbiome stability through coordinated immune regulation.

Claim	Dose	Substantiation
Supports gastrointestinal comfort Supports a healthy gut microbiome Helps support a balanced gut microbiome	100 mg	Hazan S, Daniels J, Vidal A, Peterson R, Clark A. S2149 Effect of Effera (Human-Equivalent Lactoferrin) Supplementation on the Human Gut Microbiome in Individuals With IBS. Official journal of the American College of Gastroenterology | ACG. 2025;120(10S2):S461–S462. doi:10.14309/01.ajg.0001136056.97825.3f
Supports gastrointestinal health	200 mg	Mizuki M, Tsukahara T, Oda H, et al. Effects of Lactoferrin on Prevention of Acute Gastrointestinal Symptoms in Winter: A Randomized, Double-Blinded, Placebo-Controlled Trial for Staff of Kindergartens and Nursery Schools in Japan. Int J Environ Res Public Health. Dec 21 2020;17(24)doi:10.3390/ijerph17249582
Supports beneficial changes in gut microbial composition Helps support a balanced gut microbiome	340 mg	Peterson RD, van der Made J, Donovan SM, et al. Effects of Human Lactoferrin (Effera®) at Two Doses Versus Bovine Lactoferrin on the Adult Gut Microbiome and Fecal Short-Chain Fatty Acids: a Randomized, Double-Blind Trial. Journal of Dietary Supplements. 2026/05/04 2026;23(3):415–439. doi:10.1080/19390211.2026.2673021

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