

WHEY LACTOFERRIN:

The Minor Mighty Molecule

Whey Protein & Lactoferrin

Whey protein has long been recognized as a reputable source of protein for human health and fitness. Indeed, whey protein is one of the highest quality proteins and is digested and absorbed at many locations throughout the intestine.¹ Whey protein is often used as an additional protein source for those whose diets may not contain enough or for those wanting to build more lean muscle mass. The benefits of whey protein are attributed to the diverse types of proteins which comprise it, each with unique functions lending benefits far greater than simply maintaining muscle mass.

Table 1. The Impact of Processing on Bioactive Proteins and Peptides (adapted from Korhonen et al. 1998. Trends in Food Science and Tech. 9: 307-319.)

Protein	Concentration g/L	Biological Activity
Caseins	28	Transport of ions (Ca, P ₀₄ , Fe, Zn, Cu) Precursor of bioactive peptides
B - lactoglobulin	1.3	Retinol carrier Binding of fatty acids Antioxidant
A - lactalbumin	1.2	Lactose synthesis Ca carrier Immunomodulation Anticarcinogenic
Immunoglobulins	0.7	Immune protection
Glycomacropeptide	1.2	Bifidobacteria growth Immunomodulation Antiviral
Lactoferrin	0.1	Antimicrobial, wound healing Antiviral Antioxidant Anticarcinogenic Antitoxin Antiinflammatory Antithrombotic Immunomodulation Fe absorption
Lactoperoxidase	0.03	Antimicrobial, wound healing
Lysozyme	0.0004	Antimicrobial, wound healing Synergistic effect with lactoferrin Synergistic effect with immunoglobulins

Of the approximately 32.43g of protein that are found in one liter of bovine milk, there is a minor protein present in the measly amount of 0.1 g/L, which has more recognized roles than any other milk protein¹, and may well be the most biomedically valuable.² This protein is called Lactoferrin (Lf). Lactoferrin's roles in the body exceed double that of other milk proteins, although they are all intertwined into the realm of immunity. Studies have noted lactoferrin's function as an antimicrobial, antiviral, antioxidant, anticarcinogenic, antitoxin, anti-inflammatory, and an antithrombotic¹. A plethora of studies have also documented its involvement in immunomodulation, iron sequestering and transport as well as wound healing¹. Lactoferrin is touted to be a faithful warrior as it influences the effective destruction of harmful pathogens while protecting the body against damage from excessive immune responses.^{2,3} In other words, Lf both up-regulates and suppresses immunity to protect the body from dangers, including danger from the body itself!

The Role of Lactoferrin in Immunity and Inflammation

Lactoferrin plays a vital role in the body's first line of defense and innate immunity since it is present in various secretions such as tears, nasal secretions, saliva, genital fluids, mucus, intestinal mucosa, bile and pancreatic juice.^{1,2} Innate immunity is the first, rapid, and non-specific immune defense; it includes cells such as macrophages, neutrophils, basophils, eosinophils, mastocytes and natural killer cells. Lactoferrin also plays an important role in adaptive immunity, however, its influences are indirect. Adaptive immunity is a slower yet highly specific immune defense; it may either mobilize B cells or T cells depending on the type of threat encountered.

Lactoferrin, a digested form of lactoferrin, has been noted to stimulate phagocytosis, a mechanism to remove pathogens and cell debris, by both neutrophils and macrophages in response to injury or infection.² The expression of pro-inflammatory cytokines (such as IL-1, IL-6, IL-8, TNF- α and IL-23) has been shown to be modulated by Lf.³ Cytokines, which are signaling molecules, are necessary to initiate tissue healing, however an overactive immune response created by an unregulated expression of cytokines can destroy the same tissue. One study even found that Lf attenuated the severity of an influenza-induced pneumonia response by minimizing immunity-mediated cellular infiltration and thus fluid volume.³ In another study, Lf attenuated asthma-induced airway obstruction due to

its anti-inflammatory modulation.³ Conversely, supplementation of Lf in a study done in healthy male volunteers improved immunity as measured by increased T-cell activation and hydrophilic antioxidant capacity.⁸ Using similar immune measures, another study found that in mice with both healthy and compromised immune systems, toxic infection by *T. gondii*, a single-celled parasite, was weakened.⁹

Box 1: Lactoferrin & the Immune System

Enhances Innate Immunity (Non-specific Immune Response)

- Present in mucous, tears and other body fluids where it has direct antimicrobial and antiviral effects
- Increases Neutrophil activity
- Increases Macrophage activity
- Direct antimicrobial and antiviral action in the body by depriving pathogens of iron, which they need to survive
- Prevents oxidative damage to body tissues and cells

Enhances Adaptive Immunity (Specific Immune Response)

- Increases dendritic cell activity leading to T-cell proliferation
- Increases and modulates T-cell activation and activity
- Moderates cytokine release helping to prevent the occurrence of a "cytokine storm", which results from overstimulation of the immune system

In any case, inflammation is the manifesto of immunity; hence a brief discussion on it follows. Neutrophils are often the first to respond to an assault. As they arrive on scene with increased plasma flow, they then release signals attracting other immune cells to the site; both the signaling molecules and cells further contribute to inflammation. During inflammation, neutrophils scavenge lactoferrin from the plasma and bring it to the affected tissues where Lf binds iron and inhibits iron-catalyzed oxidative damage⁷. This is evident in post-surgical patients where elevated Lactoferrin levels have been found. In fact, an investigative study found that topical talactoferrin, a human recombinant form of lactoferrin, improved the healing of neuropathic ulcers, or skin wounds, of diabetic origin.² With a less

detrimental but more common problem, researchers found that fermented milk supplemented with additional lactoferrin decreased the inflammation underlying acne vulgaris.⁶ This shows that Lf is both medically and cosmetically valuable.

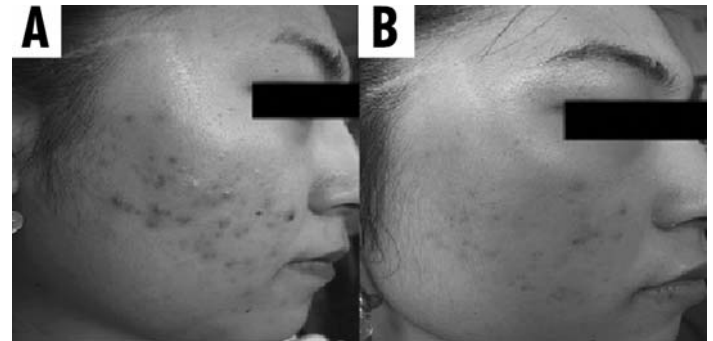


Figure 1. Decreased acne as a result of lactoferrin supplementation (from Kim et al. 2010. *Nutrition* 26: 902-909.)

Antimicrobial Actions of Lactoferrin

Lactoferrin was initially known for its ability to bind metals, or more specifically, iron. Copper, manganese, aluminum and zinc can also be bound by Lf but in smaller amounts as compared to iron.^{1,7} This could be an essential delivery system of vital minerals to a breastfeeding infant from the mother. The capacity to bind iron confers antimicrobial properties to Lf as many bacteria, parasites, and other pathogens require iron to function, so its deprivation becomes detrimental to the intruders.^{1,3}

Lactoferrin has been documented to inhibit many kinds of pathogenic microorganisms including bacteria, yeast, fungi, parasitic protozoa, and antibiotic-resistant pathogens¹. Interestingly, when digested by peptides, lactoferrin yields the bioactive component lactoferricin, perhaps a more potent antimicrobial.^{2,3} It has also been recently shown that lactoferrin contains two distinct peptide domains through which it exerts antimicrobial effects⁷; an iron-binding domain and a lipopolysaccharide (LPS) binding domain³. When Lf binds to the LPS, which is a vital component of the bacterial cell wall, it destabilizes its membrane causing the bacterium to burst.^{1,7} Another way that Lf disturbs the bacterial membrane of *E. coli* in particular, causing cell death, is by blocking porins; this inhibits the exchange of nutrients between the bacteria and its environment⁷.

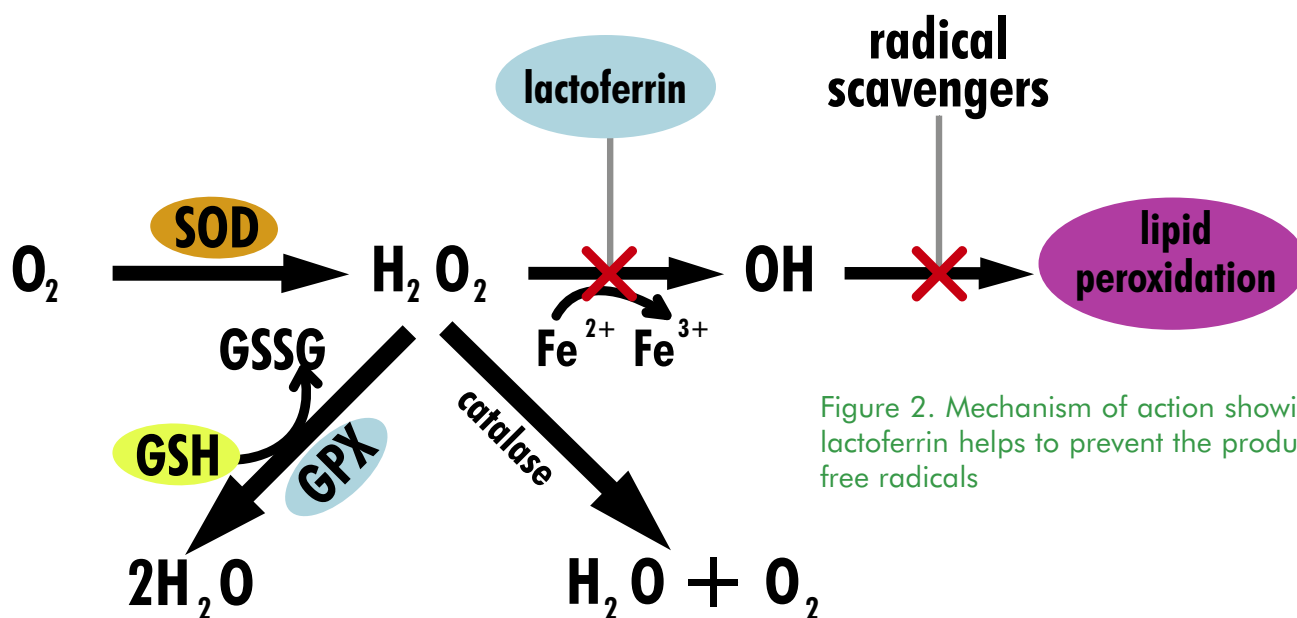


Figure 2. Mechanism of action showing how lactoferrin helps to prevent the production of free radicals

Other research has shown that Lf can also inhibit the growth of 3 types of candida fungi, including the well-known pathogen *Candida albicans*, which alternative medicine often refers to as yeast overgrowth, by depriving the yeast of iron¹⁰. Furthermore, increased interest in Lf's role in the prevention of late-onset sepsis in neonates (infection by any pathogen within the first 48 hours of life) has found Lf helpful in reducing infection of many sources and it may even assist in killing antibiotic resistant microbes that have developed due to overuse of antibiotics.^{1,4,5} In cases of helicobacter pylori (the bacteria that is a main cause of acid reflux) infection, for example, where antibiotics alone did not work, the addition of Lf to the treatment helped eradicate *H. pylori*.²

Lactoferrin may also protect the host against viruses such as HIV-1, hepatitis C and herpes in any stage of infection. In the case of HIV, not only is the replication of the virus in T-cells inhibited by Lf, but even its transmission via dendritic cells². Its mechanism of inhibition appears to be by blocking cellular receptors or by binding to the viral cell itself¹, helping prevent both viral replication and transport to other sites in the body².

On a microbe-friendly note, lactoferrin promotes the growth of certain strains of *Bifidobacteria* (probiotics) which act as biological barriers in the intestines against pathogenic bacteria.¹

Lactoferrin as an Antitoxin

As mentioned earlier, Lf binds to bacterial lipopolysaccharides (LPS), which is one of two antitoxin mechanisms exerted by Lf.³ Lipopolysaccharides are the part of the bacteria's cell wall, which are responsible for illness, thus classified as endotoxins.

When the LPS are bound by Lf, the bacteria can no longer replicate or cause endotoxic shock and illness. Such binding disturbs the bacterial membrane, causing cell lysis or death. The second antitoxin mechanism is by inhibiting the production of toxic free radicals.

Lactoferrin as an Antioxidant

This means that Lf can act as an antioxidant. Upon tissue injury or infection, reactive oxygen species, which are a form of free radicals that can be produced by free iron, are released from digested tissues or from the overactivation of immune cells.^{2,3,7,11} In addition, cytokines can be released in massive quantities due to oxidative stress, hence causing the production of more oxidants. Fortunately, neutrophils pick up Lf and bring it to the site of insult, where it binds iron, limiting oxidative species formation and thus further damage.^{1,11} Whey proteins have also been found to enhance the body's own production of natural antioxidants such as glutathione as investigated in cases of HIV, cancer and high oxidative stress.^{1,2}

The terms antioxidant and anticarcinogenic could almost be synonymous as it is well known that free radicals are associated with cancer development. Many studies have shown Lf to inhibit tumor growth and metastasis. One proposed mechanism of action is that Lf, or other whey components, may inhibit the production of GSH (growth-stimulating hormone) in cancer cells. Lactoferrin may cause selective apoptosis (cell death) of certain human cancerous cells, and when combined with chemotherapy, may completely eliminate tumors.² Other forms of cancer therapy are also enhanced when combined with Lf, such as

improving the efficiency of immunotherapy (such as dendritic cell therapy) or enhancing drug cytotoxicity to cancer cells. Supplementation with Lf has also been shown to quickly restore immunity after chemotherapy for cancer.²

Conclusion

Evidently, lactoferrin has many health benefits and has high biomedical value. It is potentially a future adjunct to treatments for cancer, autoimmune disorders, and antibiotic or antimicrobial therapy where drugs alone have failed to safely and effectively reduce the risks. The exciting part for general consumers is that lactoferrin is already a natural component in the human body, and bovine Lf is two thirds to three quarters similar in protein and DNA sequences to human lactoferrin⁷, and in some cases more efficacious. As if Lf was lacking in might on its own, other components of whey have additional powerful health benefits towards bone growth, lipid balance, blood pressure control, insulin activity, mood and cognition, to name a few.² From the origins of dairy products being nutritional staples to our current and evolving understanding of its numerous health benefits, we sure have come a long “whey”.

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- Contains 3 powerful immune system boosters
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