

ImmunoLin[®] in Sports Nutrition

Athletic Performance Starts in the Gut

ImmunoLin[®] is a protein-based (>90%) dietary supplement containing over 50% immunoglobulins that helps support digestive function and a healthy mucosal immune system. Similarly, breast milk and colostrum (milk produced immediately after birth) also contain high levels of immunoglobulins and other nutritive factors designed to benefit the newborn. ImmunoLin[®] is serum-derived bovine immunoglobulin/protein isolate (SBI) and is manufactured using a tightly-controlled and highly reproducible process at an FDA-inspected facility. Research studies provide evidence that the diversity of immunoglobulins and growth factors found in ImmunoLin[®] are safe and may help improve digestive health and nutritional status by decreasing immune activation through mechanisms that involve antigen binding and strengthening gut barrier function.



INTRODUCTION

It is widely recognized that protein feeding and resistance exercise are two of the most potent stimulators of skeletal muscle synthesis^(1,2). To boost dietary protein intake, competitive as well as recreational athletes often ingest protein supplements. This has led to the development of numerous protein supplements that are available to athletes who wish to build or retain muscle tissue and speed recovery after rigorous training sessions. Common examples of such protein supplements are powdered products prepared from whey, casein, egg, or soy.

In recent years a new wave of sports nutrition products has begun to appear in both research studies and a variety of performance enhancement products that are based on bioactive peptides or proteins. The goal of such products, besides supporting muscle protein synthesis (MPS) and exercise recovery, is to provide *additional* support for the digestive, immune, and cardiovascular systems. Bovine colostrum, for example, has received considerable attention based on studies and anecdotal evidence showing benefits for nutrient absorption, body composition, and immune function. Many of these effects are attributed to the immunoglobulins, growth factors and other bioactive proteins that are known to exist in colostrum.

Another more recent option available to athletes is the use of serum-derived bovine immunoglobulin/protein isolate (SBI) as a supplemental dietary protein to maintain healthy muscle tissue and support recovery after rigorous physical training. This protein isolate is available as the branded product ImmunoLin® and contains high levels of bovine immunoglobulins and other peptides that may help support immune function, muscle health, and recovery from strenuous exercise. The aim of this review is to provide a brief overview of SBI and summarize the evidence supporting its health benefits in comparison to other dietary proteins used in sports nutrition products by competitive and recreational athletes.

BOVINE PROTEIN SOURCES IN SPORTS NUTRITION

Protein Supplementation in Athletes

Due to the additional amino acids needed to support skeletal muscle growth, athletes who consistently engage in resistance training or athletic events typically require elevated levels of dietary protein, as compared to their non-athlete peers. Accordingly, supplementing the diet with additional protein has become very popular among athletes, both amateur and professional, who want to build muscle tissue and speed recovery after rigorous exercise. This has led to an increase in the different types of protein supplements that are available to athletes or other adults who wish to build or retain muscle tissue and shorten post-exercise recovery time.

Numerous studies have been conducted to better understand the role between dietary protein and the mechanisms involved in maintaining healthy muscle. Researchers have found that ingestion of approximately 10 g of protein after resistance exercise supported muscle protein when compared to exercise alone^(3,4). The increase in MPS that follows resistance exercise and protein feeding occurs in both younger^(2,3,5,6) and older subjects^(7,8), and is at least partly due to the postprandial rise in circulating essential amino acids following the consumption of protein⁽⁹⁾. While researchers have determined that dietary leucine, an important branched-chain amino acid also found in muscles, is a potent stimulator of MPS, a full complement of other essential amino acids, peptides or nutrients may be necessary to support optimal MPS and shorten post-exercise recovery time^(10,11).

The physiologic stress induced by high-intensity anaerobic exercise or prolonged endurance exercise is known to cause *acute depression of many components of the immune system*⁽¹¹⁾. For example, it is well-established that exercise and training have a negative impact on the overall number and/or function of different immunocompetent cells in blood. Circulating concentrations of different lymphocyte populations (e.g. CD4, CD8) decrease after long-duration physical work⁽¹²⁾. Neutrophils normally represent about 50–60% of total circulating white blood cells and are essential for host defense. Extreme exercise leads to reductions in several aspects of neutrophil function, although circulating levels are increased slightly^(13, 14). The mucosal immune system associated with the gastrointestinal or upper respiratory tract is considered by experts to be the first barrier to colonization by pathogenic microorganisms⁽¹⁵⁾. Immunoglobulins in mucosal secretions, especially the IgA subclass, are particularly important for protecting mucosal surfaces, since levels in mucosal fluids correlate more closely with resistance to upper respiratory tract infections than serum immunoglobulins. Studies have found that salivary IgA levels can decrease as much as 70% and last for several hours after completion of intense, long-duration exercise, but not after submaximal exercise^(16, 17). Unfortunately, protein sources that are traditionally used in most sports nutrition supplements may have little impact on supporting the immune system following exercise.

Bovine Milk Proteins

While both casein and whey from cow's milk have been widely used as protein sources in nutritional supplements, whey protein is currently the most popular protein used in sports nutrition products. Different processing methods are used to prepare the commercial forms of whey (or casein), which can *affect the final amino acid and peptide content and other physical properties* in commercial nutritional supplements (e.g. bioavailability, taste, mixability).

Research studies have revealed that a variety of factors associated with the source of dietary protein may influence support of muscle protein. Examples include the quantity and quality of protein ingested, the digestibility of the food source, and the insulin response to the meal⁽¹⁸⁾. Hydrolyzed preparations of milk proteins have also been commonly used in sports nutrition products because they are believed to be more rapidly digested and absorbed, which may improve postprandial plasma amino acid availability compared to intact protein^(19, 20). Other reports have suggested that whey protein may offer other health benefits that are not provided by casein, such as favorable impact on immune protection⁽²¹⁻²³⁾. One study by Lands and colleagues reported that 20 healthy young adults who took 20g/day of whey protein during 12 weeks of athletic training experienced improved immune function, performance and alterations in body composition when compared to casein⁽²⁴⁾.

Bovine Colostrum

Research studies also indicate that supplementation with colostrum, the first milk produced following birth, can help maintain healthy muscle, lean muscle mass, and maintain immune function following strenuous exercise^(25, 26). Colostrum differs from mature milk in both composition and function^(27, 28). The composition of colostrum is rather complex since it delivers a complete range of nutrients to support the growth and development of the neonate during the initial phase of its life. It contains high amounts of macronutrients, such as protein, fat and carbohydrates, and several bioactive substances that may be associated with immunological protection and development of the neonates' immune system.

Colostrum is particularly rich in *immunoglobulins*, but also contains lactoferrin, growth factors and other bioactive peptides that are important for nutrition, immunity, and growth and development. Decades of research studies have documented the critical role played by immunoglobulins in maintaining gut homeostasis and overall health. Immunoglobulins are found naturally in both colostrum and serum and play an important role in protecting against invading pathogens, promoting a healthy immune environment, and contributing to the establishment of the intestinal microbiota⁽²⁸⁻³⁰⁾. Several of the same bioactive proteins and peptides found in colostrum are now found in various dietary supplements based on the early study results showing potential benefits in helping to maintain muscle health, support immune function, and reduce post-exercise recovery.

SERUM-DERIVED BOVINE IMMUNOGLOBULIN/PROTEIN ISOLATE (SBI)

Bovine *serum* is another source of bioactive proteins and peptides, including immunoglobulins, which have been used for immunotherapeutic applications. One company (Entera Health, Ankeny, IA) has made a new and exciting product available from bovine serum known as **ImmunoLin®**. This innovative product is essentially a concentrated form of immunoglobulins along with other important bioactive peptides found naturally in bovine serum, and may represent a new cutting-edge sports supplement that may help support the immune system.

The protein isolate found in ImmunoLin® [known as serum-derived bovine immunoglobulin/protein isolate (SBI)] consists of over 60% immunoglobulins that bind to a wide array of microbial antigens or degradation products, such as bacterial endotoxin (also known as LPS) ⁽³¹⁻³³⁾. This binding action is believed to contribute to the mechanism of action of SBI by limiting the exposure of immune cells to bound antigens, which in turn helps limit the release of pro-inflammatory cytokines (e.g. TNF- α , IL-1 β , and IL-6) or other substances that may modify the immune response. This may be an important feature of a sports nutrition supplement since immune-depressive levels of proinflammatory cytokines ^(11, 34, 35) and bacterial endotoxin ^(36, 37) have been reported in the blood of athletes involved in vigorous exercise. Current opinion is that strenuous exercise leads to myofibril damage and increased gut permeability, which causes increased levels of cytokines (and endotoxin) both locally and systemically ⁽¹¹⁾. Studies have also shown that cytokines contribute to muscle protein breakdown, which could in turn delay recovery and have negative effects on MPS and performance ⁽¹¹⁾.

SBI offers several benefits, making it a superior option vs available colostrum supplements:

- o The levels of *lactose can be as much as 50 times lower* in SBI compared to other commercially available colostrum supplements (Table 1). This is of particular importance, since many people are unable to digest lactose and lactose can be associated with increased gut permeability (38) and gastrointestinal distress.
- o SBI provides the highest protein content and the *highest percentage of IgG* compared to other commercially available colostrum supplements (Table 1). The higher purity of SBI delivers the most efficient source of IgG per dose.
- o SBI contains *extremely low levels of endotoxin* compared to other commercially available colostrum supplements (Table 1). Consuming products contaminated with endotoxin will increase exposure of the intestinal mucosa to this inflammatory antigen when the tissues are already potentially compromised from vigorous exercise.
- o Because immunoglobulins and growth factors are present in higher concentrations in SBI compared to whey or casein, considerably less SBI would need to be consumed to take advantage of potential benefits for supporting immune function following exercise.

Table 1. Comparison of SBI and Representative Colostrum Products

Product Description	Serum-Derived immunoglobulin/Protein Isolate (SBI)	Immunoglobulin Concentrate from Colostral Whey Peptides	Highly Concentrated Colostrum IgG
No. lots tested	3	3	2
% Protein (w/w)	90.6 ± 1.1	72.4 ± 3.7	74.1 ± 0.9
% IgG (w/w)	52.4 ± 0.7	31.5 ± 2.9	35.3 ± 3.5
Lactose %	<0.15	8.1 ± 1.9	8.3 ± 0.7
Endotoxin (EU/mg)	0.3 ± 0.1	2.4 ± 0.5	1.8 ± 0.7

Unique manufacturing process

SBI is a spray-dried powder product obtained by fractionating edible grade bovine plasma. It has been manufacturing in a state-of-the-art, USDA-inspected facility for over 15 years. ImmunoLin is manufactured to contain a broad range of the bioactive proteins found in plasma using fractionation methods designed to enrich target proteins rather than strictly purify individual proteins. ImmunoLin is $\geq 90\%$ protein, $\leq 1.5\%$ fat, and $\leq 8\%$ water. The protein composition of SBI typically contains over 50% IgG, along with bovine serum albumin (~10%), transferrin (~6%), and IgA and IgM (~5%), and other bovine plasma proteins that are similar to those found in colostrum (Figure 1).

Scientific Studies Supporting the Mechanism of Action

Evidence from several studies suggests that the immunoglobulins and other bioactive peptides found in SBI help maintain gut barrier function by binding microbial compounds. In vitro studies have demonstrated that SBI binds to many different microbial components present in bacterial, fungal, and viral organisms, which are known to activate the intestinal immune system if allowed access through a damaged intestinal epithelium^(31, 32). This binding ability is most likely responsible for the *benefits of SBI* through a mechanism that involves immunoglobulin attachment to potentially toxic microbial antigens that appear normally in the intestinal tract due to the breakdown and turnover of resident bacteria (e.g. bacterial endotoxin) or through consumption of contaminated food or water. A study by Detzel, et al.⁽³⁹⁾ used an *in vitro* cell culture model to show that binding of antigens by the immunoglobulins in SBI prevented translocation of the antigens across epithelial cells, which in turn avoided the production of inflammatory cytokines by adjacent immune cells. These results suggest that the binding action of immunoglobulins in SBI helps keep toxic antigens within the lumen of the intestinal tract and avoid their absorption into the blood stream, which ultimately may help minimize increases in gut permeability and immune activation that occur with exposure to such antigens⁽³⁹⁾. Other peptides found in SBI may also provide benefits to support the health and integrity of the absorptive epithelial cells that line the intestinal wall.

Polyacrylamide Gel Electrophoresis

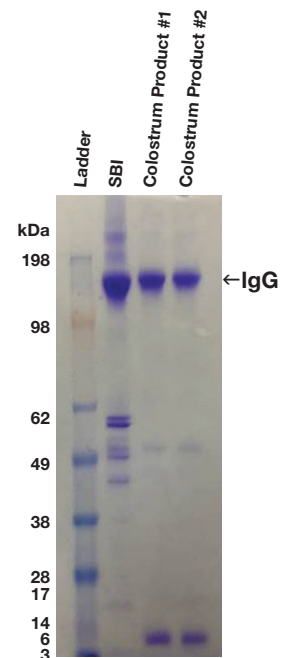


Figure 1. Protein Comparison of SBI and Representative Colostrum Products

BENEFITS OF IMMUNOLIN® RELATE TO SPORTS NUTRITION

Supports Intestinal Health

A wealth of data from research studies demonstrates that oral administration of SBI supports intestinal health and nutrient absorption. High immunoglobulin-containing serum protein preparations such as SBI have been shown to consistently improve the growth, food intake and other nutritional parameters in a variety of animal species⁽⁴⁰⁾. Torrallardona⁽⁴¹⁾ summarized the results from over 70 animal studies and showed that immunoglobulin-containing plasma protein preparations, like SBI, were safe and supported caloric intake, growth and metabolism, and utilization of nutrients following supplementation in healthy animals. Collectively, such reports have led to the extensive use of plasma protein isolates as an animal feed component since the 1980's in order to **support feed intake, nutrient utilization, and immunocompetence** of weanling domesticated animals⁽⁴²⁾.

Two animal models have been utilized to assess the effect of SBI on supporting gut barrier function. In a rodent model, SBI supplementation supported the changes in specific markers of gut barrier function⁽⁴³⁾. Consumption of SBI also led to decreased mucosal crypt permeability and helped maintain levels of certain

Daily supplementation with ImmunoLin® may help avoid immune-depressive effects of strenuous and prolonged exercise, maintain gastrointestinal health, and support muscle protein synthesis and recovery from strenuous exercise sessions.

proteins involved with mucosal barrier function (E cadherin and zona occluden-1) and protecting intestinal mucosa (muc2 and trefoil factor 3). In another study in mice⁽⁴⁴⁾ supplementation with SBI significantly maintained colon mucosal height, cecal stromal structure, and colonic glandular tissue when compared to mice treated similarly but without supplementation with SBI.

Evidence that SBI helps maintain intestinal homeostasis is also supported by results from randomized human clinical trials^(45,46,47). Two additional clinical studies assessed the effect of SBI for supporting nutritional status in infants and children. In summary, these results provide scientific evidence that **SBI helps maintain intestinal homeostasis**, which is critical for optimal nutrient utilization to support muscle.

Maintains Immune Function

The impact of SBI on immune function has also been evaluated in human clinical trials. In an early open-label study of SBI patients, SBI supplementation led to significant improvements in symptom and quality-of-life measures and increases in CD4+ counts in the duodenum⁽⁴⁶⁾. In a large multicenter, placebo-controlled follow-up study⁽⁴⁷⁾, SBI administration led to significant increases in peripheral CD4+ cells at week 4 and week 24 among subjects in the lowest quartile for baseline CD4+ cells (<418 cells/mL), when compared to subjects that received placebo. Levels of CD4+ cells and CD4+/CD8+ cell ratios were also increased in duodenal mucosal biopsies. The study also found significant decreases in circulating levels of interleukin-6 (a proinflammatory cytokine) and markers of intestinal barrier damage and enterocyte death. Authors concluded that the results support the hypothesis that binding and exclusion of gut bacterial antigens by SBI helps to support the mucosal and systemic immune functions.

Animal models have also been utilized to evaluate the effect of SBI on intestinal *immune function*. Perez-Bosque and colleagues used the mouse model described earlier and found that SBI supplementation led to significant decreases in the expression of *proinflammatory* cytokines in gut mucosal tissue, while increasing levels of certain *anti-inflammatory* peptides⁽⁵⁰⁾. SBI supplementation also led to decreases in neutrophil recruitment and activation in mesenteric lymph nodes and the lamina propria. In another study involving mice with a compromised immune function, SBI administration also resulted in significantly lower concentrations of serum markers for acute gut inflammation and epithelium damage⁽⁴⁴⁾. Plasma immunoglobulin concentrates like SBI have also been shown to help support the health status of newly weaned pigs⁽⁵¹⁾.

In summary, the results from human trials and animal studies provide evidence that SBI helps maintain a healthy immune system that has been challenged through mechanisms that may involve antigen binding and strengthening gut barrier function.

“High-intensity or prolonged endurance exercise has been shown to cause acute depression of many components of the immune system.”

– Pedersen BK, Hoffman-Goetz L
Physiological reviews.
2000; 80(3):1055-81

Other Features That May Benefit Exercise Performance (protein synthesis, etc.)

Previous studies used a mouse model of acute lung injury to show that plasma or immunoglobulin concentrates can improve the inflammatory cytokine profile and reduce the percentage of activated neutrophils and monocytes in lung airway and lung tissue^(52,53). While these results may be surprising to some, it is widely recognized that the mucosal immune systems associated with different tissues are highly interconnected. Which means that stimulation of the intestinal immune system can modulate the local immune response, which in turn may modify the immune response of other mucosal (i.e. respiratory) lymphoid tissues⁽⁵⁴⁾. Furthermore, oral immunoglobulin may also help support respiratory epithelia following extreme exercise - as well as replace the loss of salivary immunoglobulins to help avoid respiratory infections^(16,17). These results using the acute lung injury model may be important and relevant for sports nutrition products, since it implies that oral immunoglobulin concentrates like SBI may help support the bodies response beyond the GI tract.

A highly active area of investigation in sports supplement science is the pursuit of protein derivatives or peptides that are responsible for supporting MPS, muscle cell development, and muscle function. Plasma contains over 250 active peptides⁽⁵⁵⁾ and some of these are likely to play a role in support of protein metabolism and thus have an effect on the musculoskeletal system. Such bioactive peptides exist in both colostrum and plasma and can act as

signaling molecules or perform direct functions. Examples include insulin-like growth factors 1 and 2 (IgF-1, -2), transforming growth factor beta (TGF- β), epidermal growth factor (EGF), fibroblast growth factor, platelet-derived growth factor (PGF), lactoferrin, and lysozyme.

Proteomics techniques have identified over 180 unique proteins in SBI, including at least 15 immunoglobulin-related peptides. Although the data identifying the specific peptides in SBI and their possible benefits in athletes is limited, there is reason to believe that at least some bioactive peptides exist in SBI and may benefit muscle health.

Safety and Recommended Doses

The safety of SBI has been documented in clinical trials involving over 250 subjects and published retrospective chart reviews describing the use of SBI by approximately 199 subjects. In total, nearly 450 subjects/patients have been exposed to SBI for a minimum of 1 day to a maximum of 24 months with doses ranging from 5 g to 20 g per day. There are no known side effects associated with consumption of SBI.

The recommended daily dose of ImmunoLin® for athletes is 1000-2000 mg per day. ImmunoLin® doses should be supplemented twice daily (e.g. 1000 mg per dose), particularly before or after exercise sessions, resistance weight-training, or athletic endurance events. ImmunoLin® appears as a light-colored powder and consists of 500 mg of SBI. ImmunoLin® does not contain milk products such as lactose, casein, or whey, and are gluten-free, dye-free, and soy-free. ImmunoLin® is manufactured in accordance with current Good Manufacturing Practice (cGMP).

FEATURES & BENEFITS OF IMMUNOLIN®

- o Helps restore a healthy immune system that has been compromised by external stresses
- o A source of key peptides that may support health and recovery from intensive exercise sessions
- o Provides important immunoglobulins and other proteins to avoid immune-depressive effects of strenuous and prolonged exercise
- o Safety and immune benefits documented in human clinical trials
- o Sourced from all natural and high-quality materials
- o Proprietary process that preserves the quality of active immunoglobulins and other proteins
- o Non-allergenic protein source

CONCLUSION

Serum-derived bovine immunoglobulin/protein isolate (SBI) is a protein isolate found in ImmunoLin® that offers a new protein supplement option for athletes to help support muscle tissue and recovery after rigorous physical training. When compared to colostrum supplements, SBI contains higher levels of immunoglobulins, no lactose, and lower concentrations of endotoxins that can exacerbate the immune activation commonly occurs in the intestinal tract following vigorous exercise. Daily supplementation with ImmunoLin® may help avoid immune-depressive effects of strenuous and prolonged exercise, maintain gastrointestinal health, and support muscle protein and recovery from strenuous exercise sessions.

For more information please submit an inquiry
on our website located at:
www.enterahealth.com/immunolin

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