# Health Benefits of Whey Proteins

**Ranjan Sharma***
*OzScientific Pty Ltd, Melbourne, Victoria, Australia*
**Nagendra Shah**
*Victoria University, Melbourne, Victoria, Australia*

**OzScientific Pty Ltd*
*PO Box 8018, Tarneit, Victoria 3029, Australia*
*tel +61431972591 - fax +61397485584 - e-mail ranjan@ozscientific.com*

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## SUMMARY

Whey proteins have been recognized as a source of nutrients for decades and recent advances in analytical and biochemical techniques have helped characterize their bioactive potentials. Several bioactive peptides are released by proteolysis during gastrointestinal digestion or fermentation by proteolytic microorganisms. A number of commercial whey protein isolates and whey protein hydrolysates have found applications in functional foods, sports, infant foods and nutraceuticals. This review will highlight various whey based products and their health benefits.

## INTRODUCTION

Manufacture of cheese by rennet coagulation or of casein by acid precipitation results in a large amount of whey that is rich in several nutritional components. Although whey has been recognised as a source of nutrition for many years, only recent advances in analytical and biochemical techniques have helped in characterisation of its health promoting components and verification of their bioactivities. Nutritionally, whey proteins are considerably superior to plant proteins and offer one of the highest quality proteins to the food industry. Its proportion of essential amino acids, including branched-chain amino acids, is similar to the amino acid needs of the body.

Whey proteins have become popular in the area of sports nutrition, where their role to rebuild muscle after strenuous, weight-bearing exercise have been considerably scrutinised. The amino acid profile of whey is almost identical to that of skeletal muscle, and whey protein supplements generally provide a higher dose of the essential amino acids than other protein sources.

Proteins from whey also contain a range of biologically active peptides, which are encrypted within the sequence of the parent proteins, and can be released by enzymatic proteolysis, for example, during gastrointestinal digestion or during processing (**1**). Once released, bioactive peptides may act in the body as regulatory compounds with a hormone-like activity. Although many of the bioactive components from whey remain commercially unexploited, developments in new processing technologies such as membrane filtration and ion exchange chromatography have stimulated commercialisation of some of the biologically active components from whey. Concentrates of these biologically active whey proteins have now found applications in functional foods, dietary supplements, nutraceuticals, sports, infant and medical foods.

### Components of whey proteins

Milk contains approximately 0.6 to 0.7% protein as whey protein (protein not precipitated by acid or rennet) and proportionally represent approximately 20% of total milk proteins. Whey proteins offer a rich source of components that promote health benefits (***Table 1***).

**Table 1** *Approximate composition of biologically active components of whey*

| ***Component of whey*** | ***Amount*** (mg/L milk) |
|---|---|
| β-Lactoglobulin | 3.2 |
| α-Lactalbumin | 1.2 |
| Glycomacropeptide | 1.2 |
| Proteose peptone | 1.1 |
| Immunoglobulin G | 0.7 |
| Serum albumin | 0.4 |
| Lactoferrin | 0.06 |
| Immunoglobulin A | 0.04 |
| Immunoglobulin M | 0.04 |
| Lactoperoxidase | 0.03 |
| Lysozyme | 0.0004 |

β-Lactoglobulin is the major whey protein accounting for approximately half of the total whey protein in bovine milk while α-lactalbumin accounts for roughly 25%. Although glycomacropeptide (GMP) is not present in milk serum, it is released from k-casein during the rennet action of cheese milk and is available as a part of whey components. Traditionally, β-lactoglobulin, α-lactalbumin, serum albumin, immunoglobulins, and proteose-peptone fractions have been the most characterised components of whey proteins. Recently, considerable attention has been paid to biologically-active smaller components such as lactoferrin, lactoperoxidase, insulin-like growth factor and other minor proteins.

***β-Lactoglobulin***

Although β-lactoglobulin is the predominant protein in whey, it is probably not the most biologically active protein in its native or intact conformation compared with other minor proteins such as immunoglobulins and lactoferrin. Nevertheless, β-lactoglobulin is a rich source of essential amino acids and specially branched chain amino acids, which play an important role in muscle redevelopment and recovery from sports and stress fatigue. Further research on biologically active components of β-lactoglobulin such as bioactive peptides is warranted for successful commercialisation of β-lactoglobulin for health and functional foods. Besides being a source of essential and branched chain amino acids, a retinol-binding protein has been identified within β-lactoglobulin structure (**2**). This protein, a carrier of small hydrophobic molecules including retinoic acid, has the potential to modulate lymphatic responses thus playing an important role within immune functions in defending the body against the infections and spread of tumours.

***a-Lactalbumin***

The second most predominant protein of whey, α-lactalbumin is a rich source of the amino acid tryptophan, that has been shown to improve sleep quality, cognitive performance under stress, and mood under stress through the formation of neurotransmitter serotonin (**3**,**4**). Supplement of α-lactalbumin enriched whey protein has been shown to increase the ratio of plasma tryptophan to other large neutral amino acids and improve the cognitive ability (evaluated by memory tests) of high stress-vulnerable individuals.

α-Lactalbumin can also facilitate the absorption of minerals and exert antibacterial and immunomodulatory effects. Clinical trials have demonstrated significant reductions in depression after an intake of α-lactalbumin. Other trials have shown improved visual memory. Trials have also shown improved sleep patterns by increasing sleepiness, reducing sleep latency and improving morning alertness. α-Lactalbumin has also been shown to be capable of undergoing structural changes to induce apoptosis in a cancer cell line, under conditions similar to the stomach (**5**). α-Lactalbumin is rich in essential and conditionally essential amino acids and is a dominant protein in human milk. In infant formula products, adding α-lactalbumin provides a number of nutritional and physiological advantages (**6**). The high content of cysteine in α-lactalbumin is also valuable in boosting the immune system and promoting wound healing (**6**).

***Glycomacropeptide***

Glycomacropeptide (GMP) is a hydrophilic peptide (amino acid residue 102 to 169) of κ-casein that provides stability to casein micelles in milk. When rennet acts on κ-casein during the manufacture of cheese, GMP is released into the whey. GMP makes up about 15% to 20% of the whey proteins and often found in whey protein concentrates (WPCs). Recent advances in fractionation have allowed separation of GMP from cheese whey into commercial GMP-enriched ingredients. Due to the highly negative charge of GMP at low pH where whey proteins are positively charged, an ion exchange process can isolate GMP. GMP is unique among the whey proteins in that it is a glycoprotein and, thus, has an oligosaccharide chain attached to it. It also is unique because it contains no phenyalanine, tryptophan or tyrosine. GMP also has high levels of the branched-chain amino acids including leucine, isoleucine and valine.

Such composition of GMP gives it some unique characteristics that can be utilized in a variety of interesting applications. A small population has phenylketonuria (PKU), meaning they are unable to digest phenylalanine. GMP is one of the few amino-acid sources PKU patients can tolerate because the pure GMP does not contain phenylalanine (**7**).

***Lactoferrin***

Lactoferrin is an iron-binding glycoprotein present in colostrum, milk and whey. Lactoferrin is a glycoprotein and exists as a single peptide chain with a molecular weight of 77,000. It is folded into two globular units with each unit able to bind 1.4 mg of iron per gram of protein. Bovine lactoferrin is somewhat similar in structure to the human form, having approximately 70% similarity in amino acids composition. The iron-binding ability of lactoferrin is responsible for many biological functions such as bacteriostatic effect, growth-promoting effect on certain cell lines, and prevention of lipid peroxidation and promotion of iron absorption in the body (**8**). Lactoferrin is one of few proteins in whey that are positively charged at pH 7.0 (isoelectric point of approximately pH 7.9) while most other proteins are negatively charged. This feature of lactoferrin has been exploited in commercial isolation of lactoferrin. Using cation based resins; lactoferrin has been separated from other proteins from whey. Using selective salt solutions, lactoferrin can be separated from other positively charged proteins attached to the resin. Further concentration of lactoferrin is carried out using ultrafiltration and spray drying. When reduced to its purest form, it is pink in colour. Commercially, lactoferrin is available in a range of protein concentrations.

Due to the low amount present in milk and whey, the cost of separation is high and therefore, ingredient cost is high. Lactoferrin can provide several physiological functional (bioactive) properties, which are mainly derived from its ability to bind iron. Each molecule of lactoferrin can bind two atoms of iron. The main bioactive properties of lactoferrin include antibacterial and antiviral properties, antioxidant properties, immune modulation and ability to carry iron (**8**).

***Lactoperoxidase***

Lactoperoxidase is an enzyme present in colostrum, milk and whey, with a molecular weight of approximately 77.5 kDa. Bovine colostrum and milk contain about 11-45 mg/L and 13-30 mg/L lactoperoxidase respectively (**9**). In whey, lactoperoxidase constitutes approximately 0.5% of whey proteins (**10**). The biological significance of lactoperoxidase is its involvement in the natural host defence system against invading microorganisms (**11**).

Separation of lactoperoxidase from whey is based on the same principle as used for isolation of lactoferrin. Lactoperoxidase is positively charged at the normal pH of whey (isoelectric point in the pH range 9.0-10.0) and can be bound to cation exchange resins and fractionated from rest of whey proteins. Lactoperoxidase inactivates or kills a wide spectrum of microorganisms through an enzymatic action. This reaction involves two cofactors, hydrogen peroxide and thiocyanate ions, which together with lactoperoxidase constitute the lactoperoxidase (LP) system. Activation of the enzyme results in the formation of hypothiocyanite ions, which are responsible for the antimicrobial action. Commercially, lactoperoxidase is isolated from either skim milk or whey using an ion-exchange process similar to that used for isolation of lactoferrin. Lactoperoxidase when used in the form of LP system has a broad spectrum of antibacterial activity, having a bacteriostatic effect against Gram-positive bacteria and a bactericidal effect against Gram-negative microorganisms, e.g. pseudomonas, coliform, salmonella and listeria (**12**).

## Ingredients based on whey proteins

A range of whey protein based ingredients are commercially available on the market.

***Whey protein concentrates and isolates***

Commercially, concentration and purification of whey proteins using membrane processing (e.g. ultrafiltration) technologies or by ion exchange chromatography has opened highly lucrative market for whey proteins. Whey protein concentrates (WPCs) contain proteins in the range 35-80% and correspondingly reduced amounts of lactose and minerals.

Ultrafiltration uses semi-permeable membranes to separate whey components based on selective molecular weight and structure. In the process, whey is contacted with the membrane under an applied pressure. The applied pressure forces the water and the smaller molecules (minerals and lactose) through the membrane (permeate) while retaining whey protein molecules (retentate). For 80% WPC, the retentate is diluted with water (termed as diafiltration) and further concentrated through ultrafiltration. When protein content of WPC is above 90%, the products are generally known as whey protein isolates (WPIs).

Whey protein isolate is commonly manufactured by either (a) ion exchange followed by concentration and spray drying or (b) microfiltration followed by ultrafiltration and spray drying. In the manufacture of WPI by ion exchange, the pH of clarified whey is lowered to 3.0-3.5 and passed through ion exchange resins where most of the proteins are adsorbed, subsequently eluted and the pH is readjusted. The protein solution is then concentrated by evaporation, ultrafiltration or reverse osmosis and spray dried. Ion exchange process is generally carried out using a batch process. Recently, a similar but continuous ion exchange chromatographic separation process has been adopted by some companies. Continuous chromatographic method allows separation of component of mixtures down to the molecular level.

***Whey protein hydrolysates***

The enzymatic hydrolysis process produces protein ingredients designed for nutritional, dietetic and medical foods. Hydrolysed milk protein is a highly purified ingredient, and milk protein is hydrolysed under controlled conditions to obtain unique functional and nutritional properties. Whey proteins can be hydrolysed to produce protein hydrolysates with variations in the degree of hydrolysis.

During enzymatic hydrolysis, proteins are broken down into peptides of different sizes and free amino acids. Specific enzymes that allow a good control over the size of peptides and functionality of peptides formed during hydrolysis are used. Enzymatic protein hydrolysates containing short chain peptides with characteristics amino acid profiles and defined molecular size are used in specific formulations such as those used for feeding hospitalised patients. For manufacture of protein hydrolysates, milk proteins are first dispersed and solubilized in water and the pH and temperature are adjusted to the desired levels (generally to the optimum temperature for the enzyme). An appropriate enzyme is then added to the protein solution (substrate) at a certain enzyme: substrate ratio that optimises the enzymatic reaction.

Under controlled conditions, the enzyme cleaves the peptides bonds and produces the desired level of protein hydrolysis.

The hydrolysed protein is optionally processed through steps such as clarification, flavour reduction, concentration and subsequently is spray dried. Whey protein hydrolysates can be used for several bioactive or physiologically functional properties such as reduced allergenicity and antigenicity (**13**), increased protein absorption and release of bioactive peptides.

## Health benefits of whey proteins

Whey proteins and its components have shown a range of health benefits as listed in *Table 2*.

**Table 2** *Key health benefits of whey proteins*

| ***Health benefit*** |
|---|
| *Cardiovascular health* |
| *Antioxidant property* |
| *Immune modulating function* |
| *Anti-bacterial activity* |
| *Liver and lung health benefits* |
| *Bone health and osteoporosis* |
| *Muscle strength and sports nutrition* |
| *Cognitive health* |
| *Growth of probiotic bacteria and gut health* |
| *Prevention of cancers* |
| *Anti–inflammatory effects* |
| *Skin health benefits* |
| *Obesity and weight control* |
| *Prevention of diabetes* |

### *Cardiovascular health*

Whey proteins have been shown to have beneficial effects on the lipid profile in serum and liver such as modification and decrease in total lipids and triglycerides. Antihypertensive peptides (ACE-I) are produced by enzymatic proteolysis (natural digestion in the GI tract, induced enzymatic hydrolysis, milk fermentation) of whey proteins. Studies have shown a reduction in blood pressure, stress hypertension through an increase in ACE inhibitory activity from short and more hydrophobic peptides produced from whey proteins (**14**-**19**).

### *Antioxidant properties*

Whey proteins are precursor or source of glutathione (GSH) which acts as an antioxidant for reactive oxygen species (ROS) which can results in the damage of tissues, especially the neurons and glial cells in the central nervous system (**20**).

### *Immune modulating functions*

Whey proteins are unique in their ability to optimize a number of aspects of the immune system, primarily by boosting glutathione (GSH) levels in various tissues. GSH, the centrepiece of the body's antioxidant defence system, protects cells against free radical damage, pollution, toxins, infection and UV exposure.

GSH levels are typically depressed in individuals with cancer, HIV, chronic fatigue syndrome and other immune-compromising conditions.

GSH also decreases with age and may be partially responsible for diseases such as Alzheimer's disease, cataracts, Parkinson's disease and arteriosclerosis. Thus, incorporating whey proteins into the diet may protect the health of not just those with a compromised immune system but those of all ages. Whey proteins exhibit beneficial properties for human health including the acquired immune response.

Whey protein extracts from beta-lactoglobulin and alpha-lactalbumin were the main active fractions having an additive effect on neutrophils that became more responsive to a subsequent stimulation. Enhanced immune response could help in prevention of bacterial and viral infections and diseases such as gastroenteritis in children. Whey protein supplementation for athletes during intense endurance training might play a role in maintaining a healthy immune system for athletes during and after exercise and training (**21**-**25**).

### *Anti-bacterial activity*

Whey protein show effects in prevention of growth of pathogenic bacteria which could offer means of controlling the growth and recontamination of *L. monocytogenes*, *Salmonella typhimurium* and *E. coli* O157:H7 in ready-to-eat meat product by using WPI as an ingredient in protective film coating (**26**-**29**).

### *Liver and lung health benefits*

Whey protein-containing diet could suppress an increase in plasma alanine and aspartate aminotransferase activities, lactate dehydrogenase activity and bilirubin concentration, which are markers of hepatitis, and also in the concentration of hyaluronic acid, a marker of fibrosis (**30**,**31**).

### *Bone health and osteoporosis*

Results have shown that the active component in the whey protein plays an important role in bone formation and a potential therapeutic role in osteoporosis by activating osteoblasts (**32**-**34**).

The physiological activity of peptides in whey protein may be used in food additives to promote the absorption of Ca (through prevention for the formation of calcium phosphates) and prevent bone disorders (**35**).

### *Muscle strength and sports nutrition*

Whey proteins are a rich source of branched-chain amino acid (BCAA). As the demand for BCAA increases with endurance exercise, whey protein can replace these BCAAs to enhance protein synthesis and muscle growth during the recovery period.

Whey proteins are particularly effective at stimulating muscle protein synthesis rates because the amino acid profile in whey is almost identical to that of skeletal muscle. Therefore whey protein through its essential amino acids helps in skeletal muscle protein synthesis and prevention of sarcopenia (skeletal muscle wasting) after endurance exercise.

Recent studies also suggest that whey proteins can help improve lean body mass and performance in athletes on a resistance training regimen (**36**-**40**).

***Cognitive health***
Whey protein rich in alpha-lactalbumin improves cognitive performance in stress-vulnerable subjects via increased brain tryptophan and serotonin activities (**41**).

***Growth of probiotic bacteria and gut health***
Glycomacropeptides (GMPs) and whey protein concentrate can support growth of probiotic bacteria such as Bifidobacterium lactis in milk. Several probiotic bacteria have been shown to improve gut health (**42**-**44**).

***Prevention of cancers***
Dietary whey protein could lower serum C-peptide concentration and duodenal SREBP-1c mRNA abundance, and reduce the occurrence of duodenal tumours (**45**).

***Anti-inflammatory effects***
Hydrolysed whey proteins are good sources of peptides with activity to stimulate intracellular glutathione (GSH) and exert anti-inflammatory activity (**46**-**48**).

***Skin health***
Whey contains proteins that serve as potent growth stimulants for a number of mammalian cell lines in culture. These growth factors have a dramatic impact on cell growth by promoting ynthesis of DNA and protein and by inhibiting degradation of protein. Thus whey protein can help in tissue repair and also could benefit in prevention of psoriasis and ulcers (**49**,**50**).

***Obesity and weight control***
The inclusion of whey protein concentrates and glycomacropeptides (GMPs) in the diet can lead to an enhanced satiety and a decrease in food intake. GMP is a powerful stimulator of cholecystokinin (CCK), which is an appetite-suppressing hormone that plays many essential roles relating to gastrointestinal function, including the regulation of food intake (**51**-**53**).

***Prevention of diabetes***
Research data suggest that as a supplement to a fat-rich meal in patients with type 2 diabetes, whey protein seems to outperform other proteins in terms of postprandial lipemia improvement, possibly because of the formation of fewer chylomicrons or increased clearance of chylomicrons (**54**-**55**).

## CONCLUSIONS

Whey proteins harbour a range of physiologically functional components that offer several health benefits such as protection from various infections, role in tissue repair, rebuilding muscles and satiety effects for weight management. Significant research has also been carried out to support these health benefits of whey proteins and the hydrolysed forms of whey proteins. Many of the whey protein ingredients with health benefits have been successfully commercialised.

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