Dairy Council DIGEST®

March | April 2001

Volume 72
Number 2

HEALTH-ENHANCING PROPERTIES OF DAIRY INGREDIENTS

SUMMARY

Recently, the potential use of dairy ingredients in a variety of food products to enhance health has captured the attention of food scientists, producers, marketers, and consumers. Several factors are contributing to this interest in dairy ingredients. These factors include recent discoveries of bioactive roles for dairy components, especially those derived from whey, advanced technologies that efficiently isolate dairy ingredients, and consumers' interest in foods that provide specific health benefits (i.e., functional foods).

Whey, a by-product of cheesemaking, contains lactose, minerals, vitamins, protein, and traces of milkfat. Much attention is focused on whey proteins. Not only is their biological value superior to most other proteins, but whey proteins also have a high content of sulfur-containing amino acids which support antioxidant functions. Whey proteins also contain branched chain amino acids which have been established to help minimize muscle wasting under conditions of increased protein breakdown.

Experimental animal and in vitro investigations have identified a number of potential health benefits for individual whey proteins such as the following:

- Beta-lactoglobulin, the most abundant protein in whey, binds retinol (provitamin A) and has been proposed to be a transport protein for retinol.
- Alpha-lactalbumin is used in infant formula to make it more similar to human milk. This whey protein has been demonstrated to have immune-enhancing activities and be useful in sports nutrition products due to its content of branched chain amino acids.
- Immunoglobulins contribute to the immune response, thereby providing protection against foodborne illnesses.
- Lactoferrin, an iron-binding whey protein, has multiple biological functions, including increasing iron absorption and transport, protecting against pathogenic bacteria and viruses, enhancing immunity, and stimulating the growth of beneficial intestinal bacteria. Lactoferrin may also help to reduce ear infections in children. In some countries, this protein is added to infant formulas to make them more similar in protein composition to human milk.
- Lactoperoxidase, a secretory enzyme found in whey, is a natural antimicrobial agent with potential use in dental products to inhibit caries.
- Glycomacropeptide, a casein-derived protein found in cheese whey, stimulates cholecystokinin (a hormone regulating food intake), helps to reduce dental caries, and is beneficial for patients with phenylketonuria (PKU).
- Other whey components such as lactose derivatives and sphingolipids in whey lipid have health-promoting properties.

Identification of bioactive roles for specific whey ingredients lends support to their potential commercial application in functional food products. However, human clinical trials are needed to substantiate the biological activity of individual whey ingredients. With the current focus on biologically active nutritional components to promote health, opportunities for the use of dairy ingredients have never been better. Whey ingredients, especially proteins, would be particularly beneficial for infants, older adults, some patients, and athletes involved in intense activities. D

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INTRODUCTION

Today's health-conscious consumers are increasingly making food choices based on a food's ability to provide health benefits, such as enhancing body functions or reducing the risk for certain diseases (1-4). The growing market for these so-called functional foods provides unprecedented opportunities for the food industry to improve existing and/or develop new food products with unique health benefits. Many traditional dairy foods, because of their essential nutrients (e.g., calcium) and other components (e.g., conjugated linoleic acid), already achieve the goals of functional foods (5). In addition, new technologies that allow isolation, concentration, or modification of dairy ingredients, along with recent discoveries of bioactive roles for dairy ingredients, are leading food scientists and technologists to consider their application in a wide variety of food products (6,7).

Several physiologically active dairy ingredients are being recognized for their potential use in functional foods, with much attention focused on components in whey, particularly whey proteins and individual protein fractions (1,6-11). This *Digest* briefly reviews some of the emerging nutritional and health-enhancing benefits of dairy ingredients, specifically whey components. For further information, readers are referred to comprehensive reports on this subject (7-10).

COMPOSITION OF WHEY

Whey, a by-product of cheese manufacturing, contains lactose, minerals (e.g., calcium, magnesium, phosphorus), vitamins, noncasein protein (except glycomacropeptide), and traces of milkfat (7,8). Protein is currently the component of whey that produces the greatest value. Not only is the biological value of whey protein superior to most other proteins (8,12), but whey proteins also have proportionately more sulfur-containing amino acids (e.g., cysteine, methionine) (7). Sulfur amino acids help maintain levels of antioxidant peptides in the body. Cysteine is a rate-limiting amino acid for the biosynthesis of glutathione, an antioxidant, anticarcinogen, and immune stimulating sulfur-containing tripeptide (1,7,12). Compared to other protein sources, whey proteins have higher concentrations of the branched chain amino acids, L-isoleucine, L-leucine, and L-valine (7). Because branched chain amino acids help regulate muscle protein synthesis, their potential use for athletes and others aiming to achieve optimal lean muscle mass is an area of active investigation.

New technologies to isolate dairy ingredients and emerging research identifying biological roles for dairy ingredients, such as whey proteins, are leading to growing interest in their potential use in functional foods.

The following individual whey proteins, in order of decreasing concentration in whey, are potential candidates for ingredients in functional foods.

- Beta-lactoglobulin. This protein comprises 50 to 60% of total whey protein. Beta-lactoglobulin binds retinol (provitamin A) and has been proposed to be a transport protein for retinol (8). Beta-lactoglobulin is a rich source of the essential amino acid cysteine, which is important for the synthesis of glutathione (13).
- Alpha-lactalbumin. This protein accounts for about 25% of total whey protein. In the mammary gland, alpha-lactalbumin acts as the coenzyme in the biosynthesis of lactose (13). In some countries, alpha-lactalbumin is used commercially in infant formulas to make the formula more similar to human milk. In addition, alpha-lactalbumin may enhance immunity and reduce risk of some cancers (7,8). Because alpha-lactalbumin is a good source of branched chain amino acids, it may also be used in sports nutrition products (7).
- Immunoglobulins. The immunoglobulins in bovine whey (and colostrum) include IgA and secretory IgA; IgG_1, IgG_2, and IgG fragments; IgM; and IgE. This group of whey proteins provides passive immunity for infants and may stimulate immune function in adults (7,8).
- Bovine serum albumin. Bovine serum albumin binds fatty acids and other small molecules. Because of its high cysteine content, bovine serum albumin may be an important source for the production of glutathione in the liver (13).
- Lactoferrin. This iron-binding whey protein appears to have multiple biological functions. These include iron transport, antibacterial and toxin binding properties, promotion of cell growth, stimulation

Whey Protein Composition (13)

PROTEIN	CONCENTRATION (g/L milk)
Beta-Lactoglobulin	3.2
Alpha-Lactalbumin	1.2
Immunoglobulins	0.8
Bovine Serum Albumin	0.4
Lactoferrin	0.2
Lactoperoxidase	0.03

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of the growth of beneficial intestinal bacteria (e.g., *Bifidobacteria*), antioxidant properties, and immunomodulating and anti-inflammatory effects (7,8). Lactoferrin is used in infant formula in some countries to provide a formula similar in protein composition to human milk and to enhance iron absorption without causing constipation. Many of the proposed biological activities of lactoferrin are related to its iron-binding properties, although non-iron-binding activities have also been demonstrated (1,7,14).

- Lactoperoxidase. This milk enzyme is a natural antimicrobial agent with a variety of potential applications including use in dental products such as toothpaste and mouth rinses to inhibit the development of dental caries (7,8).
- Other Peptides. Whey contains peptides both present in milk and formed by the hydrolysis of various milk constituents, including casein. Glycomacropeptide (GMP), perhaps the most notable, is produced by the action of the enzyme, chymosin, on k-casein (7,8). Beneficial biological roles attributed to GMP or peptides derived from it include stimulation of cholecystokinin (a hormone regulating energy and food intake) release from intestinal cells, inhibition of platelet aggregation, and support of beneficial intestinal bacteria (i.e., *Bifidobacteria*) (7,8). In an in vitro study, GMP prevented adhesion of cariogenic bacteria to tooth surfaces, leading researchers to speculate that GMP may reduce dental caries (15). Because GMP lacks the amino acid phenylalanine, GMP has potential use as an ingredient in foods for patients with phenylketonuria (PKU). These patients are unable to metabolize phenylalanine and therefore must be provided diets free of phenylalanine (8). Peptides derived from beta-lactoglobulin in whey have antihypertensive activity in spontaneously hypertensive rats (16). Other peptides such as lactoferricin, which is derived from lactoferrin, exhibit antimicrobial activity (14).

Nonprotein components of whey such as oligosaccharides and whey lipids (sphingolipids) may be considered value-added dairy ingredients with potential commercial application in functional foods. For example, galacto-oligosaccharides act as prebiotics, or non-digestible food ingredients that selectively support the growth and/or activity of beneficial intestinal bacteria such as *Bifidobacteria* (1,7,9,17-19). Sphingolipids have been found to be biologically active, including anticarcinogenic (20-23).

Individual whey proteins have been demonstrated to stimulate the immune response and support antioxidant functions.

EMERGING HEALTH BENEFITS OF WHEY PROTEINS

The traditional role of whey proteins in foods has been to provide dietary nitrogen and amino acids (7). However, in recent years, several additional beneficial physiological roles for whey proteins have been defined or suggested, as discussed below. This scientific field is so new that most of the evidence supporting biological roles for whey proteins has been derived from experimental animal and in vitro studies.

Antibacterial and Antiviral Properties. Lactoferrin consumed in food has been reported to be effective against pathogens such as bacteria, viruses, and fungi (1,7,8,10,24). For example, lactoferrin has been demonstrated to protect against pathogens such as *Haemophilus influenzae* which causes otitis media (ear infections) in children (25). The antimicrobial effect of lactoferrin was originally linked to its iron-scavenging activity (12), but more recent evidence indicates that at least some of its antimicrobial activity is independent of iron. Bovine lactoferrin, as its peptide fragment lactoferricin (lactoferricin B), directly damages the structure and alters the permeability of gram negative bacterial outer cell membranes (26). As a result, the microbial cells lose their integrity and are killed. The question of whether lactoferricin is produced in the human stomach following intake of food supplemented with bovine lactoferrin has been positively answered in at least one adult (14).

The antimicrobial activity of lactoferricin B is greater than that of lactoferrin (14,27,28). Lactoferricin B has been demonstrated to markedly inhibit the growth of several susceptible organisms including *E. coli*, *Salmonella enteritidis*, *Klebsiella pneumoniae*, *Campylobacter jejuni*, and *Listeria monocytogenes* (7,27,29). In vitro studies indicate that bovine lactoferrin and lactoferricin may help to protect against *E. coli 0157:H7* which has been associated with large outbreaks of food-borne haemorrhagic colitis (28).

Interestingly, lactoferrin has also been found to protect against a number of different viruses, including cytomegalovirus, influenza, rotavirus, human immunodeficiency virus (HIV), herpes simplex types 1 and 2, and hepatitis C (1,8,30,31).

Immune System Stimulation. Even transient alterations in the immune system can predispose individuals to increased risk of infections and diseases such as cancer, as well as exacerbate existing diseases. Cell culture studies and in vivo investigations of experimental animals have demonstrated that whey proteins enhance non-specific and specific immune responses (7-9,32). The high concentration of cysteine and glutamate in whey proteins, which are precursors for the synthesis of glutathione, is believed to contribute to these immuno-enhancing effects (32-34).

Individual whey proteins such as lactoferrin also have the ability to modulate immune functions (7,8,35). As reviewed by German (7), investigations in laboratory animals indicate that lactoferrin stimulates humoral immune response to sheep red blood cells, promotes appropriate intestinal and peripheral specific antibody response, and modulates the production of lymphokines. A recent investigation found that lactoferrin protected mice against the lethal effects of bacterial lipopolysaccharide (LPS), a powerful endotoxin produced by gram-negative bacteria (36). Consuming lactoferrin increased the survival of mice exposed to LPS by six-fold (36). Potential immunomodulating roles for other whey proteins such as immunoglobulins and GMP have also been demonstrated (8,12).

Laboratory animal and in vitro studies indicate that whey proteins have anticarcinogenic and hypocholesterolemic effects, as well as other potential health benefits.

Antioxidant Action. By supporting antioxidant functions, whey proteins could potentially help to reduce the risk of numerous diseases including cancer and atherosclerosis (9). Whey protein is rich in cysteine and glutamate, precursors for glutathione which, in turn, mitigates oxidative stress (7,8,12, 33,34). Glutathione levels in the thymus of rats are higher in animals fed a whey protein diet than in those fed either meat or soy diets (37). Individual whey proteins such as lactoferrin also inhibit oxidation by scavenging free iron, thereby limiting its availability to catalyze oxidative reactions (8).

Anticarcinogenic Activities. Whey protein has been reported to protect against some cancers (7-9,37). In laboratory rats fed whey protein diets, fewer chemically induced colon tumors developed than in rats fed experimental diets containing casein, meat, or soy proteins (38). This effect was attributed to increased tissue concentration of glutathione, which was stimulated by the whey protein diet (33,34,38,39). However, other mechanisms may be involved (37,40).

Individual whey proteins may be anticarcinogenic. When alpha-lactalbumin was incubated with two different mammalian intestinal cell lines, cell division decreased, whereas peptides from fermented casein had no effect on cell division (41). Bovine lactoferrin may also be beneficial in the prevention of some cancers (37,42-46).

Hypocholesterolemic Effect. The effects of dietary whey protein and casein on plasma and liver cholesterol concentrations were investigated in female weanling rats fed a cholesterol-containing diet for three weeks (47). At high protein intakes, whey protein significantly lowered plasma and liver cholesterol, as well as plasma triacylglycerol levels (47).

In another investigation, standard yogurt fortified with condensed whey or lactose-hydrolyzed condensed whey and bifidus yogurts reduced total and low density lipoprotein cholesterol levels in laboratory rats (48). In contrast, whole milk and standard yogurt had no hypocholesterolemic effect (48). One in vivo investigation found that lactoferrin may act as an anti-atherogenic agent by inhibiting the accumulation of cholesterol esters in macrophages (i.e., precursors of foam cells found in early atherosclerotic lesions) (49).

Other Potential Benefits. Whey proteins may potentially provide other health benefits including support of growth, bone health, and weight control. Whey contains several known growth-supporting factors including lactoferrin which may be beneficial for the recovery of tissues following metabolic stress resulting from illness, surgery, or chemotherapy treatment (6,7,50,51). Whey minerals such as calcium, phosphorus, and magnesium support bone growth and maintenance (9). In addition, whey proteins may be beneficial for bone health (52,53). The whey peptide GMP has been reported to stimulate the release of cholecystokinin (CCK). However, further research is necessary to establish whether GMP added to food products enhances postprandial satiety and has a role in weight control.

Importance of Whey Proteins for Special Populations. Hydrolyzed whey protein-based formulas are beneficial for infants with an intolerance to cow's milk protein (7). Also, extensively hydrolyzed whey formula may help reduce excessive crying in infants (i.e., infantile colic) (54). In an effort to develop infant formulas that more closely resemble human milk, researchers are examining the potential of whey protein fractions rich in specific proteins, such as lactoferrin, for their use in infant formula (1,6,8). Lactoferrin, the main whey protein in human milk, is present at a low level in cow milk (8,13,24).

Whey proteins' unique advantages may be particularly appropriate in the diets of older adults. In laboratory mice, intake of a whey-rich diet increased the animals' longevity or survival, as well as liver and heart glutathione levels (33).

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Dairy ingredients, such as whey proteins, may be particularly beneficial for infants, older adults, some patients, and athletes. However, more research is necessary to substantiate their health benefits in humans.

Whey protein may help maintain health during later years by providing growth-supporting factors which aid the recovery of tissues damaged by injury or surgery, enhance immunity, and regulate smooth muscle cell function which favors gastrointestinal health.

Patients with acute or chronic conditions may benefit from the biological activities of whey proteins (12). Because of the ability of immunoglobulins, lactoglobulins, and bovine serum albumin to enhance immunity, intake of these whey proteins may be beneficial for patients with cancer or AIDS (12). Also, branched chain amino acids found in whey proteins are readily used by muscle for energy during stress which is important for malnourished patients or those who require a protein-restricted diet (e.g., end-stage renal disease) (12).

Branched chain amino acids in whey proteins are beneficial for athletes by helping to minimize muscle wasting under conditions of increased protein catabolism, as occurs with sustained intense exercise (e.g., a marathon) (55). Intake of branched chain amino acids prevented loss of body mass and muscle in 16 athletes who participated in a 21-day hike at high altitude (56). Also, consuming a moderate energy restricted diet rich in branched chain amino acids allowed wrestlers to lose abdominal visceral adipose tissue without compromising their high level of performance (57). These observations support the performance value of whey proteins in sports nutrition foods and beverages (7).

CONCLUSION

Whey components, particularly individual whey proteins, are emerging as high-value dairy ingredients with potential use in functional foods. New discoveries of the biological functions of dairy ingredients, along with advances in developing economical separation technologies for bioactive components of whey, provide the dairy industry with exciting opportunities in nutrition and health markets (7,8). D

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ACKNOWLEDGMENTS

National Dairy Council® assumes the responsibility for this publication. However, we would like to acknowledge the help and suggestions of the following reviewers in its preparation:

- William R. Aimutis, Ph.D.
  Vice-President, Upper Midwest Operations
  Land O'Lakes, Inc.
  St. Paul, MN
- J. Bruce German, Ph.D.
  Professor and John E. Kinsella Chair
  Department of Food Science and Technology
  University of California
  Davis, CA

The *Dairy Council Digest*® is written and edited by Lois D. McBean, M.S., R.D.

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ISSN 0011-5568