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Functional Peptides in Milk Whey: An Overview

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Summary

Whey protein is a by-product derived from the production of cheese and it has many benefits for human health that what the recent research work has shown, so it is known as a functional food. It is known that there are salt whey and sweet whey depending on the process of making cheese. Whey protein is absorbed and digested rapidly. Whey protein contains a number of bioactive components including β-lactoglobulin, α-lactalbumin, serum albumin, immunoglobulin, and lactoferrin. These components have positive effects on health such as immune improving and antioxidant characteristic that reduce hypertension, cancer, hyperlipidemia, and virus contagious. The transformation of the amino acid cysteine to glutathione can partially these effects. In addition, whey protein can cure inflammatory bowel disease (IBD). Moreover, whey protein is a rich source of branched chain amino acids, which are particularly good for athletes and sarcopenic cases. In this review, we conclude the characteristics of whey protein and the latest results related the effects of whey protein on specific conditions for human health.

Keywords: *Milk whey, Functional Peptides, Human health, lactoglobulin, α-lactalbumin, serum albumin, immunoglobulin, lactoferrin.*

Abbreviations

IBD: Inflammatory bowel disease; ACE: Angiotensin converting enzyme; GSH: Glutathione; BCAA: Branched chain amino acid; HIV: Human immunodeficiency virus; MBP: Milk basic protein; IGs: Immunoglobulins; LWPC: Low temperature processed; MW: Molecular weight; BSA: Bovine serum albumin; LPO: Lactoperoxidase; LSs: Lactoferrin; PPs: Proteose-peptone; CMP; Casienomacropeptide; GSH: Glutathione.

Introduction

Functional food is a nutritional food that has a positive effect on human health (Diplock *et al.,* 1999). The European Commission suggested this definition on the food which reduces the pathological conditions. Then the Japanese emerged this context during the 80's, due to the desire to empower the life of elderly people by prohibiting many diseases that led to increasing consuming of products which supporting by bioactive components (Arai., 1996).

Whey is a liquid producing during making cheese, produces by acid or proteolytic enzyme method (rennet enzymes). Whey proteins have a nutritional outcome, and improving the industry. Whey has a varied composition depends on the coagulation method, but the final product has approximately resemblance ingredients of more than 90% water and lots of dissolved components.

Whey can preserve people from epidemic diseases, for instance, boom in blood pressure and rate of cholesterol, so recently many scientists incline to find out its loyally effects on the human health (Horton 1995 and Siso 1996).

β-Lactoglobulin and α-Lactalbumin are whey proteins. Whey proteins appear about a fifth of milk proteins; contained 50% Lactoglobulin, 12% lactalbumin, 1 in 10 immunoglobulins, 5% serum albumin, 0.23% proteose peptones, lactoferrin (LF), and lactoperoxidase (LP) (Horton 1995 and Siso 1996).

Whey protein components and their peptide portions exhibit different bioactivity including antibacterial and antiviral influence, immune system energizing, anticarcinogenic action, and other metabolic traits (Gobetti *et al.,* 2002).

Recently, whey proteins have been used in many foods for example, ice cream, bread, and infant formula; moreover, whey proteins can replace fat in many products. Furthermore; whey proteins have a significant utilization as a muscle- structure complement (Lollo *et al.,* 2011, Josse *et al,* 2012).

Similar with other animal proteins, whey protein provides an enormous amount of branched chain amino acid (BCAA) (Salehi *et al.,* 2012), which has the ability to hydrate more than any protein, and increase the postprandial plasma BCAA amounts within minutes (Akhavan *et al.,* 2010, Akhavan *et al.,* 2014).

More recently, Jayatilake *et al.* (2014) reported that many bioactive peptides help against inflammatory bowel disease (IBD) by concentrating whey protein under low temperature processed (LWPC), that lead to improving recovery of body weight in mice, furthermore; increasing in mucin, which reduced inflammation in the colon (Jayatilake *et al*., 2014).

Whey protein preventing the cravings of intake food as an appetite suppressant and control of blood sugar (Akhavan *et al*., 2010, Akhavan., *et al*., 2014). However, many studies stated that whey protein has a wider range as a functional food to alleviate the conditions such as, hepatitis B, cancer, cardiovascular disease, human immunodeficiency virus (HIV) infection, osteoporosis and chronic stress (Marshall, 2004). Whey protein ought to assistance prohibit susceptibility to sensitiveness, which considers inborn conditions (Chandra, 2002).

A lot of amino acids composed from long whole molecules. Whey proteins have benefits such as, raised insulin like growth factor, developed answer of endocrine hormone (Akhavan., *et al.* 2010, Gaudel., *et al.* 2013), growing nitrogen reservation and exploitation (Blome., *et al.,* 2003, Saito.,2008), intracellular glutathione, and anti-aging antioxidants raise by whey protein (Athira., *et al.,* 2013, Xu R., *et al.,* 2011), increased immune function (Gahr., *et al.,* 1991 and Jensen., *et al.,*2012), developed gastrointestinal health (Zivkovic & Barile, 2011 and West *et al.,* 2012), and improved level of muscle growing (Walrand *et al.,* 2011 and Coker *et al.,* 2012). Here, the functional peptides in milk whey and their characteristics have shown from recently published research.

Composition of whey:

There are two types of whey that depends on coagulation method, which using in milk coagulation (sweet and acid whey). Thus, in acid whey, the casein coagulation at pH 4.6 at room temperature (Nakai *et al.,* 1996), however, coagulation by enzymatic action is the most popular method, so whey it is called sweet whey (Fox *et al.,* 1998 and Pintado *et al.,* 2001). Lactose is a soluble ingredient in water and represents in both sorts of whey between 70-72% of total solids, minerals 12-15% and whey protein 8-10%. Table 1 illustrates boom of calcium content in acid whey. (Morr *et al.,*1993).

Table 1. Typical composition of sweet and acid whey

Components	Sweet whey (g/L)	Acid whey (g/L)
Total solids	63.0 – 70.0	63.0 – 70.0
Lactose	46.0 – 52.0	44.0 – 46.0
Protein	6.0 – 10.0	6.0 – 8.0
Calcium	0.4 – 0.6	1.2 – 1.6
Phosphate	1.0 – 3.0	2.0 – 4.5
Lactate	2.0	6.4
Chloride	1.1	1.1

Ingredients of milk whey:

Milk has been using in feed young animals and for humans from childhood until elderly (Sgarbieri, 1996), due to the composition as a main source of protein (Miller *et al.,* 2000). Bovine milk contains 3% protein (Fox *et al.,* 1998), which 80 % are caseins and whey proteins 20% (Pihlanto-Leppälä *et al.,* 2003). β - lactoglobulin (β-Lg) and α-lactalbumin (α-La) are proteins found in whey; and proteose-peptone that produced as a result of β-casein (βCN) hydrolysis, small amounts of blood-borne proteins (including bovine serum albumin, immunoglobulins and BSA), and small molecular weight (MW) peptides, which derived from hydrolysis of casein (soluble at pH 4.6 and 20 °C) (Miller *et al.,* 2000 and Whitney., 1988). Whey proteins have amino acid profiles completely varied from caseins: they have a small portion of Glu and Pro, but a bigger fraction of sulfur-containing amino acid residues (i.e. Cys and Met). These proteins are dephosphorylated, denatured by heat, insensitive to Ca^{2+}, and liable to the intermolecular bond formation through disulfide bridges between Cys sulfhydryl groups. Some of whey proteins as illustrate in Table (2).

Table 2. Characteristics of main whey proteins

Proteins	Concentration (gL-1)	MW (kDa)	Isoelectric point (pI)
β-Lg	3 – 4	18.4	5.2
α-La	1.5	14.2	4.7 – 5.1
BSA	0.3 – 0.6	69	4.7 – 4.9
IgG, IgA, IgM	0.6 – 0.9	150 – 1000	5.5 – 8.3
Lactoperoxidase	0.006	89	9.6
Lactoferrin	0.05	78	8.0
Protease-peptone	0.5	4 – 20	
Caseinomacropeptide		7.0	

adapted from Zydney (Whitney 1988)

1- β-Lactoglobulin (β-Lg)

β-Lg considers the major whey protein, which acts 50 % of the total whey protein in cow's milk and 12 % of the total milk proteins (Fox *et al.,* 1998, Law *et al.,* 1993, Creamer *et al.,* 2003). Though it can be found in the milk of many other mammals, it is basically missing in human milk (Mohran, 1990 and Sawyer *et al.,* 2000). This is a protein, with 162 amino acid sediments in the main structure and a MW of 18.4 kDa. β-Lg exist in minimal 12 variants (A, B, C, D, DR, DYAK/E, F, G, H, I, W and X), and A variant is the most common. β-Lg its monomer has a free thiol bond and two disulfide bridges that makes β-Lg appear a static spatial structure (Nakai *et al.,* 1996); but its conformation is pH-dependent (Imafidon *et al.,* 1997), and it denatures at above 65°C (at pH 6.5), β-Lg denatures, thus giving increase to accumulate construction (Gough *et al.,* 1961).

A number of helpful nutritional and functional traits have made β-Lg become a component of choice for food and drink formulation: in reality, it holds excellent heat gelling (Chatterton *et al.,* 2006), and frothing traits, which can be used as stabilizing agents in such dairy products as yogurts and cheese spreads. This protein is challenging to gastric digestion, as is steady in the presence of acids and proteolytic enzymes (Sawyer *et al.,* 2000, Papiz *et al.,* 1986 and Barros *et al.,* 2001); hence, it tends to stay intact during passage into the stomach. It is also a wealthy source of Cys, and amino acid firmness the key role in the enduring synthesis of glutathione (GSH), three amino acids, Glu, Cys and Gly, which aid into composition of β-lg (Anderson, 1998).

2- α-Lactalbumin (α-La)

α-La views up quantitatively second in whey; it appears 20 % of all proteins in bovine whey, and 3.5 % of the total protein content of the entire milk (Fox *et al.,* 1998). It is a calcium metallo protein has 123 amino acids, with a MW of 14.4 kDa (Hiraoka *et al.,* 1980); and derived to three genetic variants (A, B and C), thus B is the most popular (Eigel *et al.,* 1984). A lot of studies indicate that α-La is more heat resistant at (pH 6.7) than β-Lg partly due to its denaturation being fickle below 75°C (Law *et al.,* 1994). However, it can be easily inserted in liquid or sticky products to raise their nutritional worth. This protein is commercially used in supplements for infant formula; because it is similar in composition to human milk (α-La) with its high content of Cys, Trp, Ile, Leu and Val, which make it necessary choice in sport supplements (Heine *et al.,* 1991, Tolkach *et al.,* 2005 and Walzem *et al.,* 2002). This protein has been studied more than any proteins with regard to study stability of protein mechanism (Chang *et al.,* 2 000); at low pH (Dolgikh *et al.,* 1985), high temperature (Vanderheeren *et al.,* 1994), or average concentrations of denaturants – e.g. guanidine hydrochloride (Kuwajima, 1989), α-La adopts a conformational structure called molten globule. A partly revealed state, the apo-state, is formative at neutral pH into elimination of Ca^{2+} by ethylene diamine tetracetic acid (EDTA) (Kuwajima *et al.,* 1985 and Kuwajima, 1996); this state saves its secondary, but not its tertiary structure (Dolgikh *et al.,* 1981).

α-La holds a high fraction of its native secondary structure when it is in a molten globule state of, as well as anelastic third structure (Kuwajima, 1989, Dolgikh *et al.,* 1981 and Ptitsyn 1995); it as illustrates as middle between native and unfolded states (Kinsella *et al.,* 1989 and De Wit, 1989).

3- Bovine serum albumin (BSA)

Bovine serum albumin is derived from the blood, and appearsabout 0.7-1.3 % of whole whey proteins (Nakai *et al.,* 1996). Its structure is 582 amino acid remains, 69kDa of MW, and represents 17 disulfide groups and one free sulphydryl group (Fox, 1998). BSA can link free fatty acids with other lipids due to its bulk and higher levels of structure, as well as combinations of flavor (Kinsella *et al.,* 1989), however, this trait is strictly restrainedin denaturation. Increasing the heat temperature-prompted gelation at pH 6.5 is started by intermolecular thiol-disulphide exchange, such as what happens with β-Lg (De Wit *et al.,* 1989).

4- Immunoglobulins (IGs)

Immunoglobulins found by 1.9-3.3 % in milk proteins, similar to BSA, also derived from blood serum (Nakai *et al.,* 1996); IGs constitute an intricate gathering, the components of which are created by β-lymphocytes. Igs include three different variants: IgM, IgA and IgG (IgG1 and IgG2). IgG1 consider the primary, Ig present in cow's milk and colostrum (Nakai *et al.,* 1996), while IgA is prevalent in human milk. Igs have a physiological action to give different sorts of invulnerability to the body. The whole Ig, or antibody molecule has 180 kDa for MW (Korhonen *et al.,* 2000). Igs are partially resistant to proteolytic enzymes, and are in specific activated by gastric acids (Korhonen *et al.,* 2000).

5- Lactoperoxidase (LPO)

Lactoperoxidase (LPO) is a glycoprotein which exists in colostrum, milk, numerous of other human and animal secretions (Kussendrager *et al.,* 2000). LPO is the most copious protein in whey and has exhibited antibacterial effcts over a range of animal groups. Its belongings are connected to its capacity to lessen hydrogen peroxide by stimulating the peroxidation of thiocyanate and certain halides (counting iodine and bromium) (Björck *et al.,* 1978). Lactoperoxidase seems to have the characteristics of a steady protective, opposing inactivation amid the pasteurization process.

6- Lactoferrin (LSs)

Lactoferrin is not heme iron-bound glycoprotein with antibacterial and antioxidant impacts (Caccavo *et al.,* 2002, Gutteridge *et al.,* 1981). LFs are single-chain polypeptides with 2 bound sites for ferrous ions, whey lactoferrin shows to spend its impacts by organizing transport and imbibitions iron in the gut of young people (Német *et al.,* 1985).

7- Proteose-peptones (PPs)

PPS acts 10 % of whey protein content; it is accounted for by the whey protein portion soluble after soaring heat to 95 °C for 30 min, then acidification to pH 4.6 (Alais, 1984), PPs created from hydrolysis of casein.

8- Caseinomacropeptide (CMP)

CMP is a heterogeneous polypeptide portion got from the cleavage of Phe105-Met106 in κcasein (κ-CN). At the point when milk is hydrolyzed with chymosin amid cheesemaking, thus κ-CN is hydrolyzed into two segments: one stays in the cheese (para-κ-CN) and the other (CMP) is missing in whey; the last is moderately little, with 63 remnants and a MW of ca. 8 kDa (Delfour *et al.,* 1965). Further to its polymorphisms, CMP might exist in different structures relying upon the degree of post-transcriptional transforms: it glycosylates through an O-glycoside connect, and phosphorylates by means of a Ser deposit. Note that post-transcriptional adjustments of κ -CN happen only in the CMP bit of the molecule.

The amino arrangement of CMP is surely understood; it needs aromatic amino acid deposits (Phe, Trp and Tyr) and Arg, however a few acidic and hydroxyl amino acids are available (*Manso & Lopez* 2004). CMP from dairy animals is soluble at pH in the reach 1-10, with a base dissolvability (88 %) between pH 1 and 5 (Chobert *et al.,* 1989 and Moreno *et al.,* 2002). CMP seems to remain basically solvent after warmth treatment at 80-95 °C for 15 min at pH 4 and 7 (Moreno *et al.,* 2002). Its emulsifying action shows a base close to the isoelectric point (Dolgikh *et al.,* 1981). Dziuba and Minkiewicz (1996), illustrated that a decrease in pH prompts a diminishing in CMP volume, attributable to decrease of interior electrostatic strengths and steric repugnance; this evidently has a significant impact on its emuls.

Therapeutic benefits

Milk whey includes a high amount of bioactive components such as, lactoferrin, immunoglobulins, lactalbumin and glutamine. Whey milk protein has been used to cure a lot of diseases as a therapy.

High blood pressure

Many people have been suffering from hypertension, which is a public health issue, and likely it increases cardiovascular disease risk. A lot of researchers have suggested that bioactive peptides that created during food protein hydrolysis have the capacity to prohibit angiotensin converting enzyme (ACE), and this topic has been studied in some studies (FitzGerald *et al.,* 2004, Pal *et al.,* 2010, Kawase *et al.,* 2000, Sharpe *et al.,* 1994, Xu *et al.,* 2008 and Martínez-Maqueda *et al.,* 2012). Indeed, that a diet loaded in foods, including antihypertensive peptides is efficient for the protection and curing of hypertension as it has been alleged. ACE inhibitor peptides might be gained from precursor food proteins through enzymatic hydrolysis (Korhonen *et al.,* 2003, Hartmann *et al.,* 2007 and FitzGerald *et al.,* 2004). However, studies on whey peptides and their using as ACE inhibitor activities are very few; this might be because the stout structure of β-lactoglobulin, which makes it especially resistant to digestive enzymes. ACE inhibitor peptides can plummet blood pressure in a process regulated to a limited expand by rennin angiotensin framework; renin is a protease enzyme, which is discharged because of different physiological boosts that cuts the protein angiotensinogen to deliver the idle decapeptide angiotensin I. Furthermore; ACE follows up on the kallikrein-kinin framework, catalyzing the debasement of the nonapeptidebradykinin, which is a vasodilator (Kang *et al*., 2003), and ACE inhibitor peptides apply a hypotensive effect by avoiding angiotensin II arrangement and the corruption of bradykinin.

Cancer (Conjugation of α-La with oleic acid yield a complex of potential anti carcinogenic effect)

The anti-cancer possibility of whey has tested on a lot of animals, believed that associated with the detoxifying, antioxidizing and immune-developmentalimpacts of GSH and lactoferrin (Marshall, 2004). In the existence of lactoferrin, colon malignancy in rats saw lessened tumor expression while the metastasis of essential tumors in mice were restrained (Sekine *et al.,* 1997 and Yoo *et al.,* 1998). The consequences of an in vitro study have also empowered, exhibiting the restraint of a portion of the vital strides in breast cancer advancement when treated with bovine serum albumin, in spite of the fact that the components were not completely comprehended (Duarte *et al.,* 2011). Some clinical trials have been studied, suggesting that elevated amounts of GSH in tumor cells give imperviousness to chemotherapeutic agents. Solely one of these researches illustrated that 20 patients with level IV malignancies were treated every day with 40 g whey in blend with supplements, for example, ascorbic acid and a multi-vitamin/mineral formulation (See *et al.,* 2002). The 16 survivors demonstrated expanded levels of normal executioner cell capacity, GSH, hemoglobin, and hematocrit 6 months after the fact. An exacerbate combination of immune active nutraceuticals was efficient in significantly soaringnormal killer duty, other immune parameters and plasma hemoglobin with delayed-stagecancers in patients.

Hepatitis ~~B~~

The consequences of attempts for the hepatitis B virus have been positive, especially those from an open search that included 8 volunteers dispensed 12 g whey/day (Watanabe *et al.,* 2000). The liver function of the patients has enhanced, reduced serum lipid peroxidase levels, and empowered interleukin-2 and normalkiller cell activity. Toward-hepatitis C, many trials have achieved inconclusive, despite an earlyin vitro study found that cow lactoferrin prohibit the hepatitis C virus in a human hepatocyte line (Ikeda *et al*., 1998).

Human immundeficiency virus (HIV)

Some studies have discussed to seek a therapy for human immunodeficiency virus for patients with HIV commonly have small levels of GSH by examining if whey protein could encourage beneficial impacts on the GSH levels in HIV-positive patients.18 entrants, for instance, were randomized to eat doses of 45g whey protein every day from 2 varied products over a 6-month period. Merely one of the products significantly increased GSH levels, as a consequence that might be interrelated with creation at varies insulation temperatures and non-similar amino acid sequences (Baruchel *et al.,* 1993).

Cardiovascular disease

The results of a number of works stated, consumption of milk and milk products can decrease blood pressure and plummet the peril of hypertension (Marshall, 2004). Some scientists performed an 8-week attempt in which 20 healthy males were given a blend of fermented milk and whey protein concentrate and tested the influence on serum lipids and blood pressure (Kawase *et al.,* 2000). Next 8 weeks, the fermented milk combination viewed relatively higher high-density lipoproteins, lesser triglycerides, and reducing systolic blood pressure.

Osteoporosis

Recently, some scientists proved that there are intricate associations between milk, dairy foods and osteoporosis (Caroli *et al.,* 2011). A part of whey that illustrates the capability to not only restrain bone resorption, but also encourage proliferation and differentiation of osteoblastic cells, is milk basic protein (MBP) (Marshall, 2004). Lactoferrin and lactoperoxidase existing in milk protein. Animal research supposed that lactoferrin might be the key active component, mediating its impacts through 2 major pathways: LRP1, a low-density lipoprotein receptor–linked protein, which moves lactoferrin into the cytoplasm of main osteoblasts through endocytosis, and p42/44 MAPK, which encourages osteoblast action (Naot *et al.,* 2005). Calcium has a role to determine bone mineral cluster is well renowned to be the most crucial nutritional reason to attain summit bone group, in addition, milk protein issignificant for prohibiting osteoporosis. Clinical tests maintain milk protein's positive impacts in both males and females, the last ranging in age from childhood to postmenopausal. Daily doses of 40 mg MBP (equal to 400–800 ml milk) show to be sufficient to appreciably-raise bone mineral density and plummet bone absorption (Toba *et al.,* 2001, Seto *et al.,* 2007 and Uenishi *et al.,* 2007).

Inflammatory bowel disease (IBD)

Inflammatory bowel disease is an autoimmune infection of unfamiliar etiology and can lead to inflammation and cancer. Bioactive peptides, which arein whey, contain many with possible health benefits against IBD. Jayatilake *et al.* (2014) revealed the impact of low-temperature-processed whey protein concentrate (LWPC) on the inhibition of IBD by using a dextran sodium sulfate (DSS)- prompted colitis model in BALB/c mice. Oral consumption of LWPC viewed in enhanced revival of body weight in mice. Histological analysis represented that the epithelium cells of LWPC-treated mice were recovered and that lymphocyte infiltration was plummeted. The increase in mucin due to the LWPC also resulted in decreased inflammation in the colon. Transcriptome results of the colon by DNA microarrays showed marked down regulation of genes correlated to immune responses in LWPC-fed mice. Particularly, the expression of interferon gamma receptor 2 (Ifngr2) and guanylate- binding proteins (GBPs) was increased by DSSaction and reduced in LWPC-fed mice. These results suggest that LWPCs restrain DSS-induced inflammation in the colon by curbing the signaling of these cytokines. Their findings think that LWPCs would be an efficient food resource for restraining IBD symptoms (Akhavan *et al.,* 2014).

Conclusion

Milk and milk by-products like whey act one of the primary functional foods available to folks. Many scientists have been attracted to study and scrutinize the function of whey protein for several reasons. Hence, they reached to results not provide a clear evidence regarding its use as a therapy. In the future, whey protein will be likely to result in helpful changes to human health and cure many patient diseases.

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الببتيدات الوظيفية في شرش اللبن

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الملخص

بروتينات الشرش هو منتج ثانوي من صناعه الجبن وله العديد من الفوائد لصحة الإنسان وهذا ما اظهرته الأبحاث الحديثة لذلك هو معروف كغذاء وظيفي. ومن المعروف أن هناك الشرش المملح والشرش الغير مملح او الشرش الحلو وهذا يتوقف على طريقه صناعه الجبن. من خواص بروتينات الشرش انها سهله الامتصاص والهضم. الشرش يحتوي على عدد من المكونات النشطة بما في ذلك β-لاكتوجلوبولين، α- لاكتوالبومين، الالبيومينات المناعيه، واللاكتوفيرين .

هذه المكونات لها آثار إيجابية على الصحة مثل تحسين المناعة وتعمل كمضادات الأكسدة التي تقلل من ارتفاع ضغط الدم والسرطان والعديد من الامراض ويفسر ذلك التحول من السيستين إلى الجلوتاثيون. وبالإضافة إلى ذلك، بروتينات الشرش يمكن ان تدخل فى علاج مرض التهاب الأمعاء. كما ان الشرش هو مصدر غني من الأحماض الأمينية المتفرعة، والتي هي مناسبه بشكل خاص للرياضيين وحالات اخرى في هذه المقالة العلمية، سوف نوضح خصائص بروتينات الشرش وأحدث النتائج المتعلقة بهذه البروتينات وعلاقتها واهميتها على صحة الانسان.