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Health Benefits of Whey Protein: A Review

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Abstract: Whey, a component of milk, is co-product of cheese-making and casein manufacture in the dairy industry. Nowadays, whey is recognized as a value-added ingredient in many food products. Whey and whey components are viewed as value-added ingredients in infant formulas, sports nutrition foods and beverages, and other food products. Recognition of whey as a source of diverse biologically active compounds with unique physiological and functional attributes provides opportunities for the food industry to develop functional foods or foods that have potential health benefits. Whey-derived bioactive components have antimicrobial and antiviral properties, and enhance immune defense and bone health, and improve antioxidative activity, and help protect against cancer and cardiovascular disease, and enhance the performance of physically active individuals, among other benefits. The present review is an attempt to cover scientific aspects of whey proteins' health benefits and critique some of the important research findings associated with them to date.

Key words: Whey, protein, nutrition, health benefit.

1. Introduction

Drinking milk is a practice that dates back to the domestication of animals in prehistoric times, and has taken advantage of the extensive nutritional value of that natural product. However, one major part of milk-whey, has traditionally not been paid as much attention as happened with source milk, probably because it is a by-product of cheese making, viewed for a long time as of little value. Interestingly, Hippocrates already applauded the health properties of whey in Ancient Greece; and during the Middle Age, whey was considered not only as a medicine, but also even as an aphrodisiac and a skin balm: it was in fact a regular component of salves and potions to soothe burns, to inspire vitality and to cure various illnesses [1, 2]. Moreover, whey protein, an excellent protein, is chosen by individuals of all ages who value the role of a healthy diet in helping to maintain and improve their health. Indeed, there are references to various health benefits of whey in Italian Literature dating back to early 17th century [3].

Now we detail at whey protein system, we can see that whey protein, 20% of total milk protein, consists of several different proteins, including β-lactoglobulin (β-LG), α-lactalbumin (α-LA), the heavy-and light-chain immunoglobulins (Igs), bovine serum albumin (BSA), lactoferrin (LF), lactoperoxidase, and glycomacropeptide (GMP) [4]. Whey may also include the proteose-peptone components and low-molecular weight products formed by the enzymatic degradation of the caseins during the cheesemaking process [5]. Whey protein contains all 20 amino acids and all nine essential amino acids, and it is a rich and balanced source of the sulphur amino acids that serve a critical role as antioxidants as precursors to the potent intracellular antioxidant glutathione and in one-carbon metabolism [6]. It contains three to four times more bioavailable cysteine than other proteins. Cysteine is important for the

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biosynthesis of glutathione, a tripeptide with antioxidant, anticarcinogen, and immune stimulatory properties. It also plays a key role in the regulation of whole body protein metabolism, which results in changes in body composition [7, 8]. Leucine is a particularly important factor in tissue growth and repair [9]. Leucine, isoleucine, and valine are thought to play a role as metabolic regulators in protein and glucose homoeostasis and lipid metabolism, and play a role in weight control [7, 10-13].

Currently, the biological activity of some of the minor whey proteins and peptides that can be isolated is actively studied. Current evidence for the potential of whey proteins and peptides to have health benefits beyond basic nutrition, that is to act as functional foods/food ingredients, arises from a number of sources. Emerging research findings largely from *in vitro*, experimental animals and limited human studies suggest a number of beneficial bioactivities of whey and whey components. Whey protein supplemention has many proven benefits [14]. Now, this review can helped us to describe health benefits of whey proteins and it will focus on the most recent research advances pertaining to the biological properties of whey proteins to date.

2. Antimicrobial and Antiviral Activities

Milk proteins contain many biologically active proteins. Protein and peptides, in milk, specifically whey, show promise as antibacterial and antiviral modifiers. Whey contains several components which may protect against toxins, bacteria, and viruses. These components include Igs, LF and its peptide derivative, lactoferricin, lactoperoxidase, GMP and sphingolipids [15, 16]. Furthermore, antimicrobial peptides may be generated from whey protein by proteolysis during gastrointestinal transit [17]. LF, α-LA and β-LG have been assayed for inhibitory activity aganist human immunodeficiency virus type-1 (HIV-1) [18]. In particular, ß-LG may be potential agents for preventing transmission of genital herpesvirus infections as well as the spread of HIV [19]. LF and lactoferricin inhibit a diverse range of microorganisms including gram-negative bacteria, gram-positive bacteria, yeast, fungi and parasitic protozoa [20]. It has been shown to inhibit the growth of some harmful foodborne pathogens such as *E. coli* and Listeria monocytogenes [16]. LF also shows significant antiviral activity against human immunodeficiency virus, human cytomegalovirus (HCMV), herpes viruses, human papillomavirus (HPV), alphavirus and hepatitis C, B and G viruses, among others. In addition, LF is effective aganist several non-enveloped viruses like rotavirus, enterovirus, paliovirus (PV), adenovirus and feline calicivirus (FCV) [21]. It can enhance the antibacterial activity of lysozme [22]. The antimicrobial role of LF is of particular interest to intestinal function and in the prevention of gastroenteric diseases through control of intestinal microflora. While LF exhibits bactericidal activity aganist pathogens such as coliforms, it also provides probiotic support for benifical microorganisms such as Bifidobacteria and *Lactobacilli* ssp. [23]. *Helicobacter pylori* is known as the causative agent in the majority of duodenal ulcers. It is believed to be responsible for 50%-60% of all gastric carcinomas. A number of studies have reported that daily administration of LF positively suppresses gut colonization of Helicobacter pylori in infected subjects [24]. Whey protein activates immune cell and/or prevents infection. Whey protein shows promise to help combat rotaviral diarrhea, which is a common infection that results in the death of nearly 500,000 children annually [25]. Recent studies have shown that whey protein (α-LA) fed infants had no diarrhea [26]. The natural antimicrobial action of lactoperoxidase is being used in a range of oral healthcare products and is finding application in such products directed toward the preventation and treatment of xerostimia (dry mouth). The lactoperoxidase containing products have been clinically proven to inhibit harmful microorganisms

associated with gingivitis and oral irritation, to promote the healing of bleeding gums and reduce inflammation, and combat both the causes and effects of halitosis (bad breath) [27]. *In vitro*, findings are indicated that the whey-derived sphingolipids, sphingosine and lysosphingolmyelin, have antimicrobial activity [28]. Glutathione protects the cells against free radical damage during exercise [29]. Also, it could potentially decrease infection in HIV infected children. Whey protein can stimulate glutathione synthesis. Oral whey protein supplementation increases glutathione levels in HIV infected children. Whey protein concentrate supplementation can possibly decrease the occurrence of associated co-infections [30]. Caseinophosphopeptides and GMP inhibit growth of cariogenic bacteria. Glycomacropeptide inhibits streptococcus mutans [31]. One study demonstrated that the inclusion of specific immunoglobulins in a food product may extend the shelf life of the product while it also helping in the prevention of dental caries and oral infections [32].

3. Immune Modulating Activity

Whey products and its components are shown to participate in host immunity [33]. Whey contains bioactive components that may offer protection against infections and viruses, enhance immunity, protect against some cancers. In particular, three whey peptides are known to boost the immune system by increasing production of glutathione (α-LA, β-LG and LF). Growth factors known as IgF-I and IgF-II promote gut health and wound healing [34]. Immune response is the highest in dietary whey protein. A number of whey proteins (α-LA, β-LG, LF) have been cited for their immunomodulatory effects on the body's immune system. Immune respone of whey protein (α-LA) was higher than casein, soy or whey protein [35]. LF is secreted by neutrophils and can stimulate the growth of various cells of the immune defense system including lymphocytes, macrophages/monocytes, humoral immune response, and antibody response [36]. GMP, κ-casein f (106-169), is a highly biologically active peptide that has the ability to modulate immune function [37]. Whey proteins contain some immunomodulating peptides which can be released by enzymatic digestion. Identification and isolation of these bioactive peptides could provide insights into the preparation of potent immunomodulating products [38]. α-Lactorphin, α-LA f (50-53), and β-LG f (102-105), β-lactorphin also act as ACE (angiotensin converting enzyme) inhibitors [39]. Enzymatic hydrolates of α-LA have the ability to bind calcium, copper, iron, magnesium, manganese, phosphorus and zinc [40]. LF has shown to play a major role in iron regulation in mammals. Another advantage to the use of iron-saturated LF observed in the human trial was that it did not produce any of the common side effects of iron supplements such as stomach pain, cramps [41].

4. Anticancinogenic Properties

Cancer patients undergoing radiation or chemotherapy often have difficulty in meeting their daily nutritional requirements due to nausea and lack of appetite. Whey protein is an excellent protein choice for cancer patients as it is very easy to digest and very gentle to the system [42, 43]. Whey proteins and peptides, as well as the other whey components, may protect against some cancers [33]. Diets supplemented with lactoferrin or with β-LG enhance protection aganist the devolopment of putative tumor precursors. The mechanism behind the apparent anticancer activity of dietary whey protein in these studies may be related to their sulfur amino acid contents (cysteine, methionine) [44]. Whey protein is more protective against development of intestinal tumors. Dairy proteins, particularly whey offers protection against intestinal induced tumors when compared to other protein sources. Diets containing whey have been shown to reduce intestinal, mammary, and colon cancers [45]. Total dietary whey protein was

demostrated to have a protective effect aganist the development of colon cancer in the young rat when compared with other common proteins, including casein, meat and soy. Intracellular concentration of glutathione, an anticarcinogenic tripeptide, measured in liver, was greatest in whey protein and casein. Whey is a source of precursors (cysteine-rich proteins) for glutathione synthesis and it may be important in providing protection to the host by stimulating glutathione synthesis [46]. Whey proteins contain other critical components with proven health benefits. Its low molecular weight peptides are natural antioxidants potentiators that may protect body tissues from aging and certain cancers [47]. In a vitro study, whey protein isolate enhanced the effectiveness of an anticancer drug [48]. Among individual whey proteins, attention has focused on the cancer inhibitory effect of LF and lactoferricin. In laboratory animals given chemical carcinogens, bovine lactoferrin has been shown to significantly inhibit colon, esophagus, lung, and bladder cancers when administered orally in the post-initiation stage [49, 50]. When human prostate epithelial cells were treated with whey protein isolate, intracellular levels of glutathione dramatically increased [51]. Sphingomyelin and other sphingolipids suppress colon tumor development in animal experiments [52]. A variety of studies suggest a beneficial role for calcium against some cancers [53]. Whey proteins combat skin cancer. Treatment with topical α-lactalbumin-oleic acid has a beneficial and lasting effect on skin papillomas [54]. BSA may also display anticancer activity. Breast cancer in human is inhibited by several commerical BSA preparations during *in vitro* cell culture [55]. Mader et al. [56] also demonstrated that the nature of both synthetic and pepsin-generated lactoferricin B is against human leukemia and carcinoma cell lines (Colon, breast, and ovary).

5. Cardiovascular Health

Whey proteins potentially improve cardiovascular health. Milk peptides help lower high blood pressure [57]. Fermented milk with whey protein concentrate lowers triglyceride levels in the blood [58]. Also, whey protein improves blood pressure and vascular function in overweight and obese individuals [59]. Wang et al. [60] repoted that β-LG had the ability to bind cholesterol. Futhermore, LF was reported to significantly inhibit the accumulation of cellular cholestery esters in macrophages by acting as a scavenger in a vitro study. Hydrolyzed whey protein isolate reduced blood pressure and cholesterol [61]. Whey peptides have been shown to inhibit the activity of ACE. ACE converts the inactive angiotensin I hormone into angiotensin II which constricts vascular smooth muscle thereby, increasing blood pressure. Inhibition of ACE lowers blood pressure. 20 g dose of hydrolyzed whey protein isolate decreases blood pressure and it increases white blood cell count. It also decreases low-density lipoprotein (LDL) cholesterol [62]. Whey protein exhibits anti-hypertensive effects. β-lactosin B from a commercial whey product is a new anti-hypertensive peptide [63]. They stated that whey protein supplementation has the potential to be used as an added component in dietary plans and in functional foods aimed in the management of the metabolic syndrome risk factors

6. Physical Performance

Whey and whey components offer several benefits for individuals with physically active lifestyles according to a review [64]. Whey protein is a rich source of branched chain amino acids (BCAAs), containing the highest known levels of any natural food source. BCAAs are important for athletes since unlike the other essential amino acids, they are metabolized directly into muscle tissue and these are the first ones used during periods of exercise and resistance training. Whey protein provides the body with BCAAs to replenish decreased levels and start repairing and rebuilding lean muscle tissue. Essential amino acids and whey protein are equally effective in stimulating muscle protein synthesis in elderly

individuals [65]. These amino acids provide an energy source during endurance exercise which allows athletes to train more intensively for longer periods of time [66]. Moreover, whey protein is an excellent source of the essential amino acid, leucine. Leucine is important for athletes as it plays a key role in promoting muscle protein synthesis and muscle growth. Research has shown that individuals who exercise benefit from diets high in leucine and have more lean muscle tissue and less body fat compared to individuals whose diet contains lower levels of leucine. Whey protein is easy to digest protein and is efficiently absorbed into the body. It is often referred to as a "fast" protein for its ability to quickly provide nourishment to muscles [29]. Indeed, its consumption has been shown to result in faster muscle protein synthesis as compared to other proteins. This makes whey protein more effective than other proteins for repairing exercise-related muscle damage and building bigger, stronger muscles. Its consumption results in a higher peak amino acid concentration in the blood than other proteins [67]. Whey proteins are rich in the amino acids, arginine and lysine, which may increase the release of growth hormone, a stimulator of muscle growth. Whey protein cans creatine showing an increase in lean muscle fiber adaptations [68]. Milk protein is better than soy protein for greater gains in lean mass and greater muscle hypertrophy. 20 g of whey protein casein switches net amino acid balance to positive after ingestion. It influences muscular power and strength and increase intracellular glutathione. It increases net protein gain. The rate of protein digestion affects protein gain differently during aging in humans. Whey protein is digested faster than casein. Faster digestion gives rise to a quicker amino acid flood into muscle cells. Whey protein is the preferred protein for net protein gain [69]. Dietary protein and resistance training affect muscle body composition in older persons. Adequate intake of protein combats sarcopenia. Resistance training helps older people gain muscle, hypertrophy muscle, and increase whole body fat-free mass. Adequate intake of protein and resistant exercise synergistically can reduce sarcopenia [70].

7. Weight Management

Studies show that achieving and maintaining a healthy weight can add years to your life and help prevent weight related complications, including diabetes, cancer and heart disease. Diet plays a key role in any weight management program and adding whey protein often helps make a positive difference. Whey protein is a good choice for diabetics who need to carefully manage food intake. It has potential as an added component in dietary plans and in functional foods aimed at control of appetite and body weight and in the management of the metabolic consequences of excess body fat. It has potential as physiologically functional food component for persons with obesity and its co-morbidities (hypertension, type II diabetes, hyper-and dislipidemia) [71]. It is the best protein for fat loss during energy restricted diets, when combined with exercise [72]. It improves body composition and reduces waist circumference. The researchers found that individuals who consumed whey protein weighed less, had less body fat [73]. Whey protein is the best protein for fat loss during energy restricted diets [72]. It influences on appetite and hunger controlling hormones [74]. A high-protein diet reduces energy intake and adiposity and that whey protein is more effective than red meat in reducing body weight gain and increasing insulin sensitivity [75]. In addition, whey protein helps control blood glucose levels and has been shown to be beneficial for weight management, both of which are often a concern for type-II diabetics. The meal with α-lactalbumin preserves lipid oxidation and rapidly delivers amino acids for use during exercise improved the efficiency of exercise training to decrease adiposity [76].

8. Bone Health

Milk contains several components effective for

bone health. Milk basic protein promotes bone formation and suppresses bone resorption in healthy adult men. Milk basic protein is in the whey protein fraction. 300 mg of milk basic protein increases serum osteocalcin concentrations. Milk basic protein promotes bone formation and suppresses bone resorption [77]. The milk basic protein of whey is the active protein that activates osteoblast. The active component in the whey protein plays an important role in bone formation by activating osteoblasts [78]. LF is a potent regulator of bone cell activity and increases bone formation *in vivo*. It increases osteoblast differentiation and forms new bone formation. It also decreases bone breakdown [79]. It has powerful anabolic, differentiating and anti-apoptotic effects on osteoblasts, and inhibits osteoclastogenesis. It is a potential therapeutic target in bone disorders such as osteoporosis and possibly an important physiological regulator of bone growth [80]. Glycomacropeptide has shown inhibitory activity to enamel demineralization and promotes tooth enamel remineralization [31]. Some whey components (e.g., proteose-peptones) may protect against tooth tissue demineralization, and other whey components, because of their immunostimulatory effects, may have favorable effects on dental plaque [81].

9. Other Health Benefits

An imbalance in brain serotonin levels is a possible factor manifesting the negative effects of chronic stress, fatigue, and delirium [82]. α-LA, a whey protein in cow's milk with a high content of tryptophan (a precursor of serotonin) improves cognitive performance (i.e. memory scanning) in stress-vulnerable individuals. α-LA rich whey protein increases serotonin activity. Stressed individuals were less stressed when they fed α-LA [83]. It reduces sleepiness and improves attention processes [84]. Infant formula based on predigested (hydrolyzed) whey protein is little less allergenic than standard infant formula and possibly decrease the risk that the infant will later develop allergies [85]. Whey protein is often the preferred choice for high protein products recommended by physicians following surgery or burn therapy. Whey protein contains many of the same components found in human breast milk and for this reason, it is a key ingredient in a wide variety of infant formulas, including those for premature infants. In addition, whey protein is an excellent protein choice for the expectant mother who needs increased amounts of protein. Whey protein concentrate protects gastric mucosa from ethanol damage. The protective properties are due to sulfhydyl compounds, stimulators of glutathione synthesis [86]. Whey protein is digested quickly and provides a quick rise in plasma amino acids [87].

10. Conclusion

The above review summarizes the results of research undertaken to date. In some cases, the benefits of the active peptides were demonstrated in human and animal trials. The health benefits of whey protein and whey proteins have been a subject of growing commercial interest in the context of health-promoting functional foods. Whey components, particulary the proteins and peptides, will incresingly be preferred as ingredients for functional foods and nutraceuticals as active medical agents. They built upon the strong consumer trends for health and wellbeing, and continuing discovery and substantiation of the biological functionalty of whey constituents. As a result, we are likely see major developments by the food and healthcare sectors in the widespread application of whey proteins and their associated peptides as functional food ingredients, nutraceuticals, and dietary supplements.

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