Whey protein supplement: an exclusive food or need of the hour: review

Abstract

Background: Protein is an essential portion of food that exerts beneficial effects on body composition and metabolism. However, protein-rich foods are costly and scarcely available in developing countries, and protein deficiency is a major public health concern. In this situation, searching for additional dietary protein sources is of utmost importance due to decreasing resources because of the growing global population. The current review of literature is about the cheapest, readily available unused protein source.

Methods: Milk is formed of two proteins, casein and whey. Whey is different from the casein in milk and is formed as a by-product of the cheese-making process. Whey (the liquid left after milk curdling) was deemed a waste by the dairy industry for decades, but it proved the cheapest protein source for the poor growing population in developing countries. Whey protein a complete protein as it contains all nine essential amino acids. It is low in lactose content.

Conclusion: Human body cannot make essential amino acids, so it is necessary to get enough of them from the diet. Due to the availability of carbohydrates, fat, immunoglobulins, lactose, and minerals, including essential amino acids in whey protein, it is an important source of domesticated animals' energy. There are many benefits related to whey protein consumption, such as muscle building and loss of fat. New possible therapeutic properties of whey protein have to be investigated further for the full utility to humans.

Keywords: Whey protein, milk, casein, cheapest protein

Introduction

Milk is a major source of nutrition that is widely consumed for human health. This can be obtained from several domesticated animals like sheep, goat, buffalo, and cow. Fresh cow milk consists of approximately 3.5% total protein, 80 % casein, 15% whey protein, vitamins, and lipids. These are needed ingredients for growth (Foegeding EA et al. 2002; Marshall K .2004). In other words, milk is a source of energy (carbohydrate), lactose (sugar), nitrogen (protein; subcomponents of micro fractions), and calcium (for bones)(Lollo PC et al. 2011; Josse AR. 2012). The dairy industry was treating whey (the liquid left after milk curdling) waste for decades. As whey liquid is highly organic with high biological oxygen demand, its disposal is complicated.

Commented [WPS1]: I do not think this is the right term. 'Beneficial' means something good to the body, but whose ingestion is not obligatory. Proteins are necessary to the body, so, I suggest changing this section.

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If the authors are referring to whey, this statement is incorrect. Whey is already widely used as a protein source, such as supplements. In this sense, this section should be rewritten accordingly.

Commented [WPS3]: It is not recent the acknowledgment of whey as a valuable product by the industry. If possible, add the approximate decade in which whey stopped to be considered as a waste.

Commented [WPS4]: "lactose, minerals, and aminoacids, including…"

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Commented [WPS7]: In the introduction, the authors focused on bioactive molecules, rather than on the nutritional uses and potentialities of whey per se. I suggest dividing the introduction into two parts:
One – focusing the nutritional aspects and potential of whey only relative to its protein content and composition
Two – focusing on the bioactive molecules that whey also has beyond the amino acids, and addressing the potentialities.

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Commented [WPS9]: How can the milk have 3.5% total protein and 15% whey protein? Please, correct.

Commented [WPS10]: Nitrogen is only important because it is present in proteins. I suggest highlighting the importance of amino acids and proteins, rather than nitrogen itself.

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Whey is full of biologically active components, e.g., lactoferrin, lactoperoxidase, lysozyme, immunoglobulins, etc. and is also having antimicrobial properties(Lollo PC et al. 2011; Josse AR. 2012). Milk is formed of two proteins, casein and whey. Whey protein is often separated from the casein in milk or created as a by-product of cheese making. It is beneficial in wound healing due to high protein contents, weight loss as no fat, in infant health as full of amino acids. It is an excellent protein for all age groups, especially for marasmus children, and maintains their health(Athira Set al.2013;Xu R 2011). The human body cannot make essential amino acids, so it is vital to get enough of them from the diet. Due to the availability of carbohydrates, fat, immunoglobulins, lactose, and minerals, including essential amino acids in whey protein, it is a vital source of domesticated animals' energy (Blome RM. 2003).

Whey protein may be a popular fitness and dietary supplement. It is prepared from whey, which is the liquid that separates from milk during the cheese-making process. Whey protein powder can be prepared by drying filtered whey liquid. Whey protein may be a popular choice among athletes, fitness enthusiasts, and other people eager to build muscle or reduce fat. Studies show it can help recovery from exercise, muscle building and even help lose weight by reducing appetite and boosting metabolism (Marshall K .2004; Lollo PC et al. 2011; Josse AR. 2012). The whey protein can be taken by mixing it with water or with other liquid of choice. Despite its health benefits, some people are concerned about their safety. The whey protein concentration is different in different animals as sheep and goats have similar concentration but higher than bovine (cow) whey.

These days, industries present whey protein as a health supplement in place of various health food and beverages. These proteins are used for medicinal purposes and improve the health status of all age groups of humans. This protein is usually involved in controlling or maintaining blood glucose levels and provides additional benefits, including weight management(Mortensen LS et al. 2009). Whey liquid is obtained from the milk of different domesticated animals, and then whey liquid is purified by removing several constituents (Saito T. (2008). There are three types of whey, i.e., whey protein concentrate (WPC; the low but still substantial level of fat and cholesterol; higher bioactive components), whey protein isolate (WPI; remove fat and lactose content but lower in bioactivated combinations), and whey protein hydrolysate (WPH; pre-digested and hydrolyzed; hydrolyzed whey could also be less allergenic). Besides, there are many immunological components in whey protein (Athira Set al.2013; Xu R 2011; Blome RM. 2003; Mortensen LS et

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Commented [WPS14]: The authors should introduce the term ‘essential amino acid’ before addressing it. Not all readers are aware of this term.

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al. 2009; Saito T. 2008). Despite its health benefits, some people are concerned about their safety and side effects.

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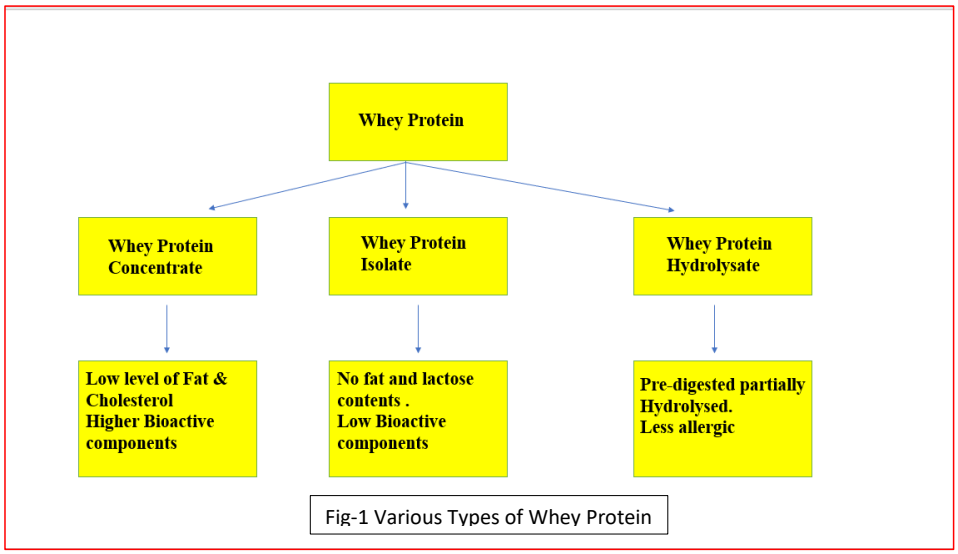

Fig-1 Various Types of Whey Protein

Amino acid content is an essential factor in bovine milk proteins, especially caseins and whey protein. In contrast, milk protein is a potential source of immunobiologically active peptides full of nutritional value. Whey protein provides all those essential amino acids which a human cannot produce itself within the body. These amino acids are nine in number with a different function. These amino acids fulfil all body requirements and keep the body fit with lean muscle mass (Coker RH et al. 2012; Burd NA. 2011). Branched-chain amino acids, e.g., leucine, isoleucine, and valine, are also present in whey. These branched-chain amino acids help in protein synthesis and thus cover up to one-third of muscle protein. Besides, only these amino acids are not degraded in the liver, but other amino acids are normally regulated by the gut and the liver. Consuming these branched-chain amino acids before physical workup can upsurge uptake into the muscle tissue and provides many profits, e.g. enhanced growth hormone circulation; lower lactate levels and better muscular oxidation; decrease serum concentrations of intramuscular

Commented [WPS17]: Here is the explanation about essential amino acids. It should be placed at the start of the introduction, where there is a recommendation for explaining what an 'essential amino acid' is.

Moreover, it would be interesting to cite the nine essential amino acids.

enzymes creatine kinase and lactate dehydrogenase etc.(De Bandt JP et al. 2006; Luigi F. et al. 2016). The branched amino acids are released from the liver and other internal organs to skeletal muscle. The blood sugar levels can be controlled by branched-aminoacids.

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Thus about 40-50 % of blood sugar during exercise is produced with branched amino acids (De Bandt JP et al. 2006; Luigi F. et al., .2016). Cysteine and methionine, which help to grow immune function through intracellular conversion to glutathione, are present in high whey protein concentrations (Grimble RF et al., .1998). Lactoferrin (iron-binding glycoprotein) contains about 689 amino acid residues and its concentration in human milk (2mg/ml) and colostrums (7mg/ml), respectively; while in bovine milk (0.2mg/ml) and colostrums (1.5mg/ml) respectively (Gupta A, Chaphalkar SR (2016; Gupta A, Chaphalkar SR .2016). The lactoferrin acts as an antimicrobial and anti-inflammatory agent and can induce natural killer cells and colony-stimulating factors, including macrophages' activation (Gupta A, Chaphalkar SR (2016; Gupta A, Chaphalkar SR .2016). In small children less than two years of age, lactoferrin is delivered through breast milk. Nowadays, bovine lactoferrin, including recombinant human lactoferrin, is obtainable commercially and is usually added to various food products, including milk, useful for the immune system. The lactoferrin possesses antibacterial and antiviral activities in the intestine against multiple pathogens. Besides, it may regulate the iron content of infants and pregnant women via a receptor-mediated pathway.

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Whey protein also contains immunoglobulins (blood group proteins)that are useful for enhancing immunity. The highest concentration of these immunoglobulins is present in colostrum (first milk after birth). As per the literature, immunoglobulins help various bacterial infections and exist in the form of antibodies (i.e., IgG, IgM, IgA, and secretory IgA; Ig stands for Immunoglobulin)(Bell SJ. 2000). These immunoglobulins deliver passive maternal immunity to infants through breast milk and help to maintain our immune system. These immunoglobulins are about 10-15% of total whey proteins from bovine milk(Bell SJ. 2000). The colostrum of cow, sheep, and bovine is full of lactoferrin (Gupta A, Chaphalkar SR (2016; Gupta A, Chaphalkar SR, .2016). Bovine milk contains the enzyme lactoperoxidase, which has antibacterial properties against many pathogens. This enzyme, in combination with hydrogen peroxide (H_2O_2) and thiocyanate (SCN^-), works as an antimicrobial agent in raw milk samples (Steele WF.1969;

Björck L. et al. .1975; Shin K et al. 2001). Whey contains lactalbumin, one of the significant milk serum proteins, i.e. alpha-lactalbumin, which has antiproliferative effects in human cell lines, especially in adenocarcinoma as Caco-2 and HT29. The content of alpha-lactalbumin is much higher in cow's milk and may cause an allergic reaction in some cases(Kelleher SL et al. 2003; Ren J.1993). Goat milk free of allergic reaction is thus useful in young children. The concentration of alpha-lactalbumin is different in different animals, e.g., cow (52.9-53.6 %), sheep (8.97-17%), and goat (13.31-34.7%) (Kelleher SL et al. 2003; Ren J.1993; Abrahão V. 2012).

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Various health benefits of whey proteins

Commented [WPS24]: Although interesting, several of the properties explored in the subsections are associated with one or two works. Considering this is a review work, an extensive search for other studies is strongly advised since it is not possible to establish an effect with only one or two studies unless it is a full clinical study up to at least phase III.

In this sense, I recommend merging all subsections and present the findings in an extensive and comprehensive table with adequate discussion, rather than 'salami slicing' the potential properties in subsections without giving the proper in-depth to them.

Whey protein is a cheap and readily available protein source in developing countries like India. It is full of many benefits to human beings in its various derivative forms (concentrate, isolate, and hydrolysate).

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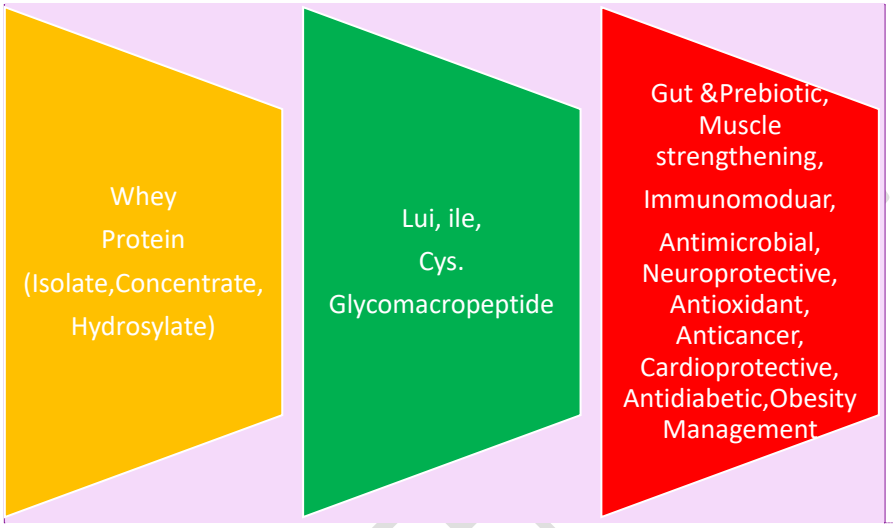
Fig-2 Benefits of whey protein

Figure-3 showing the health benefits of whey proteins in various forms



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Gut and Prebiotic action

In seriously-ill patients, the gut does not function appropriately and becomes unable to absorb even a bland diet. This affects the health of patients. The high cost is the biggest barrier for parenteral nutrition to all such patients. In these patients, whey protein protection might impart inflammation and enhance enteral nutrition (Abrahão 2012). To exert their therapeutic property, lactic acid bacteria and yeast need to be viable. The prebiotic action of whey on the gut may be not that effective due to the hostile gastrointestinal environment and whey storage. Whey protein gels can encapsulate the protecting the microbes, and their efficacy is increased against adverse conditions. The encapsulating Lactobacillus rhamnosus CRL 1505 in whey protein and pectin survive better at low pH.

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Similarly, pectin beads with a whey protein layer could be used as a probiotic carrier in acidic functional foods(Gerez et al., 2012). Lactobacillus acidophilus and Bifidobacterium in yoghurt beverages are stabilized with high-methoxyl pectin and whey protein concentrate(Walsh et al., 2014). This proves the role of whey as probiotics and prebiotics stabilizer. Whey protein isolate

and alginate microparticles have shown appropriateness as oral delivery systems for probiotic yeast Saccharomyces boulardii (Hébrard et al. 2010).

Muscle Strengthening

All eccentric and concentric skeletal muscle exercises result in muscle damage and produce inflammatory markers (muscle proteins in the blood)(Morton et al. 2009). The anabolic protein hydrolysates and amino acid supplements accelerate the repair. Leucine-derived metabolite β-hydroxy-β-methyl butyrate ingestion results in the healing of muscle injury. Resistance exercise, such as weight-lifting, raises oxidation products in plasma disturbs leukocyte redistribution and leukocyte functionality(Freidenreich and Volek 2012). The whey protein diet is better than the casein diet to heal injuries sustained due to isometric and concentric exercises. (Martin et al., 2013). The low-protein (6.25 g) beverage can be as effective as a high-protein dose (25 g) at stimulating myofibrillar protein synthesis rates when supplemented with a high (5 g) leucine content(Churchward-Venne et al. 2014). Leucine, an amino acid (10 % of the total whey amino acid), is essential for muscle hypertrophy. Health parameters, performance, and body composition effects produced by a 12-week intake of hydrolyzed whey protein were compared in players. Ingestion of the hydrolyzed whey protein helped drop in the muscle damage markers (creatine kinase and lactate dehydrogenase) (Lollo et al. 2014). Lean body mass gains are significantly high in whey protein consumers than soy protein, and this is due to the high levels of leucine and faster absorption (Volek et al., 2013).

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Immunomodulator Action

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This may be applied to the following subsections.

Whey protein concentrates on enhancing essential mucosal immunity during early life and has a protective role in some immune disorders(Pérez-Cano et al. 2007). The incidence of atopic dermatitis (a chronic skin disease characterized by swollen, scaly, and itchy rashes) is increasing worldwide, with infants being a major vulnerable group. A meta-analysis of the systematic review revealed that atopic dermatitis incidence was considerably lower among infants in the partially hydrolyzed whey-based formula group than the bovine milk group(Alexander et al. 2010). The finding suggested that whey-based formula might protect infants from atopic dermatitis. Psoriasis is chronic autoimmune disease-causing thick skin, dry scales, and red patches. Bioactive whey protein isolate can decrease systemic inflammation due to psoriasis by increasing glutathione levels. The intake of 20 g/day whey protein isolates improved Psoriatic patients (Prussick et al., 2013).

Antioxidant Action

Inflammatory or oxidative stress can cause cystic fibrosis, pneumonia, diabetes, cancer, atherosclerosis, myocardial infarction, ageing, and many other degenerative diseases (Essick and Sam 2010). Whey is full of the antioxidant glutathione and can eradicate the adverse effects of the stressors. Hyperbaric treatment of whey protein accelerated the release of bioactive peptides, raised intracellular glutathione level, and decreased the in vitro generation of interleukin IL-8, a cytokine responsible for respiratory tract diseases(Piccolomini et al. 2012). The dietary supplementation of pressurized whey (20 g/day) in cystic fibrosis patients decreases serum C-reactive protein level significantly (Lands et al. 2010). The antioxidant and anti-inflammatory

Commented [WPS31]: What stressors?

effects of pressurized whey protein isolate and native hydrolysate in human epithelial colorectal adenocarcinoma Caco-2 cells exposed to H_2O_2 were compared(Piccolomini et al. 2012). The results suggested that whey protein isolate hydrolysates can alleviate inflammation and oxidative stress in intestinal cells exposed to oxidative injury, further enhanced by their hyperbaric treatment. The consumption of whey protein hydrolysate boosts HSP70 expression (De Moura et al., 2013). Thus the whey protein hydrolysate can enhance cell survival factors such as HSP90 and vascular endothelial growth factor (VEGF)(Moura et al., 2014). Pressurized whey protein can decrease the level of the inflammatory response, oxidative stress, and lung damage. Thus whey protein subjected to hyperbaric treatment has superior biological attributes. It protects the airway proteins from oxidation and stimulating leukocytes to kill the pathogens and save them from Pseudomonas aeruginosa(Kishta et al., 2013). Whey protein hydrolysate has an antioxidant effect against paracetamol-induced hepato-nephrotoxicity(Athira et al., 2013).

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Anticancer Action

Several studies have suggested that whey protein hydrolysate may help treat cancer patients and thus improve the anticancer efficacy in cancer of the colon (Attaallah et al. 2012). (Castro et al. , 2009;Takata et al. , 2001). A 48-year-old female patient with increased serum levels of leucine, isoleucine, valine, lysine, threonine was administered with whey protein (10 g thrice daily) and a weekly intramuscular injection of testosterone enanthate before and during the standard-of-care (SOC) chemotherapy. As a result of the combination therapy, improved lean body mass, physical activity, and overall quality of life were observed in recurrent cervical cancer (Dillon et al., 2012).

Cardioprotective

Whey protein intake reduces cardiovascular disease (ischemic stroke) risk. Whey-derived extract (NOP-47) ingestion increased impaired brachial artery flow-mediated dilation (improved endothelial function). Postprandial plasma amino acids level increased. Arterial dilation improvement was independent of circulating vasoactive compounds such as nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factors. The cardiovascular risk might be lessened by using rapid-absorbable extracts derived from whey(Ballard et al., 2013). (Sheikholeslami Vatani and Ahmadi Kani Golzar 2012).

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Antidiabetic Action

Diabetes affects all human organs accompanied by many complications such as loss of vision, angiopathy, reduced blood flow leading to tissue hypoxia, and nonhealing ulcers(Casqueiro et al. 2012). Type-2 diabetes is managed by diet control and hypoglycaemic drugs. Whey protein has been demonstrated to reduce serum glucose levels in healthy individuals, maintain muscle mass, boost the release of satiety hormones (cholecystokinin, leptin, and glucagon-like peptide 1 (GLP-1)) and lower the secretion of the hunger hormone ghrelin (Sousa et al. 2012). For ancillary therapy in glycemia and vascular inflammation control in people with diabetes, cysteine in whey protein is quite useful(Jain 2012).

The whey protein helps in diabetic wound healing by restricting inflammatory cytokines' access by maintaining standard IL-10, TNF-α, IL-1β, and IL-6 levels. High serum levels of leucine, isoleucine, valine, lysine, and threonine induce Insulin secretion in the body (Badr et al. 2012a; Salehi et al. 2012).

Whey protein fractions (whey isolate and whey hydrolysate) added to a fat-rich meal lowered postprandial triglyceride responses in type 2 diabetic subjects. Both components provoked a higher insulin response(Mortensen et al., 2012). A hydrolyzed whey protein-based supplement may result in a higher leucine level, followed by an increased insulin level (Toedebusch et al., 2012).

Obesity Management

Whey protein helps in the reduction of obesity. The ameliorating effects of the protein-rich diet on metabolic disorders are precisely due to the modulation of satiety mediated by liver lipogenesis attenuation(Freudenberg et al., 2013). The whey protein concentrate employs more substantial beneficial effects than that of soy protein isolate on appetite, calorie intake, anthropometry (body mass index and waist circumference), and body composition (body fat mass and lean muscle) of obese men and thus reduce obesity (Tahavorgar et al. 2014).

Side Effects of Whey Protein: -

Whey protein is a beneficial nutritional food, and there is no other natural protein equivalent to this. Still, there can be risks from nutritionally refined foods such as whey, as it is a heavy protein. Acne can develop if a person takes whey protein for a long time. Most whey protein's side effects are related to digestion and may experience bloating, gas, stomach cramps, and diarrhoea. But most of these side effects are due to lactose intolerance due to lack of the enzyme lactase required to digest lactose.
Moreover, lactose intolerance is quite common, and about 75% of people are affected worldwide. In such cases, whey protein isolate powder can be used as a whey protein isolate is more refined. It contains a smaller amount of fat and lactose than whey protein concentrate.

People with a cow's milk allergy may be allergic to whey protein. Cow milk allergy exists up to the initial three-year age, and after that,90% of people outgrow cow's milk allergies. A cow's milk allergy symptoms are hives, rashes, facial swelling, throat, tongue swelling, a runny or stuffy nose, and rarely anaphylaxis, a severe, life-threatening allergic reaction.

Interaction with Drugs

Levodopa-Whey protein interferes with the absorption levodopa and thus decrease the effectiveness of levodopa. So, avoid taking whey protein and levodopa together.

Albendazole -Whey protein interferes with absorption and can decrease albendazole absorption in the body and decrease albendazole's effectiveness. So avoid taking both together.

Alendronate-Whey protein can decrease the absorption and effectiveness of Alendronate. So, avoid taking whey protein within two hours of taking Alendronate.

Antibiotics (Quinolone antibiotics). Whey protein and antibiotics should not be taken together due to decreased absorption. Don't take whey protein supplements and tetracycline together, and a gap of one hour is essential. Other antibiotics that might interrelate with whey protein are Quinolone antibiotics such as ciprofloxacin, norfloxacin, sparfloxacin, etc.

Commented [WPS35]: This section should be addressed earlier in the paper (in the introduction) since the safety problems are very important and should be assessed before the evaluation of any therapeutic property.

Commented [WPS36]: Please, add the proper citations for this section.

Commented [WPS37]: It is strongly suggested to transform this section into a table compiling the information; if possible, add more interactions. A comprehensive discussion of the findings and patterns is also strongly suggested. Moreover, there are no citations. Please, add them.

This issue should be addressed in the safety assessment, taking into account that the effects of drug interactions are paramount for the secure use of whey in people under medications.

Antibiotics (Tetracycline antibiotics)- As whey protein contains calcium that can attach to tetracyclines in the stomach and decrease tetracyclines' absorption. To avoid this interaction, take whey protein four hours after taking tetracyclines.

Conclusion

Whey protein is an essential and economical protein source full of nine amino acids and branched amino acids. So, it is a first-rate nutrient. Only whey protein can fulfil the increasing demand for an economical protein source for humans in developing nations. Various forms of whey protein can be used as a health supplement. Excess of everything is bad, so is whey protein. Whey protein is full of immunoglobulins and can challenge cancer as an immune-nutrient. Still, whey is an underutilized resource, and new strategies should be planned to increase its utility for human welfare.

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Bell SJ Whey protein concentrates with and without immunoglobulins: a review. *J Med Food* 2000; **3(1):**1-13.

Commented [WPS38]: The authors stated throughout the entire paper that whey is an economic protein source, but no economic data is presented. I recommend the authors adding economic data in the introduction to prove this statement and strengthen the entire paper.

Commented [WPS39]: In the present form, the conclusion does not bring anything of special, nothing 'definitive'.

The conclusion should be better written, focusing on the key findings that render whey suitable as a protein source, but also addressing potential risks and opportunities relative to this material.

Commented [WPS40]: Most of the references are before 2015, and the newest ones are from 2016. Whey is a current research topic in several areas, including medicine. I do not believe that there aren't any newer studies than 2016.

I strongly advise the authors to carry out an extensive literature review and add current (after 2016) references. In the present form, the paper loses its entire novelty and may end up missing important new findings and insights in the area; and this is exactly the objective of a review.

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