Whey Protein: A Functional Food
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Introduction
Whey protein, with its high protein quality score and high percentage of BCAAs (branched chain amino acids), has long been popular in the exercise industry as a muscle-building supplement. However, research suggests it may have far wider applications as a functional food in the management of conditions such as cancer, hepatitis B, HIV, cardiovascular disease, osteoporosis and even chronic stress.

Whey Protein Production
Whey protein is extracted from whey, the liquid material created as a by-product of cheese production. Advances in processing technology have resulted in a number of different finished whey products with varying nutritional profiles. These are summarised in Table 1 which is has been extracted from K. Marshall’s ‘Therapeutic Applications of Whey Protein’.

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Protein Concentration</th>
<th>Fat, Lactose, Mineral Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whey Protein Isolate</td>
<td>90-95%</td>
<td>Negligible</td>
</tr>
<tr>
<td>Whey Protein Concentrate</td>
<td>May range from 25-89%</td>
<td>Some fat / lactose / minerals which decrease as protein concentration increases</td>
</tr>
<tr>
<td>Hydrolysed Whey Protein</td>
<td>Variable</td>
<td>Varies with protein concentration</td>
</tr>
<tr>
<td>Undenatured Whey Concentrate</td>
<td>Variable</td>
<td>Some fat / lactose / minerals which decrease as protein concentration increases</td>
</tr>
</tbody>
</table>

Table 1: Commercially Available Whey Proteins
|                        | higher amounts of immunoglobulins and lactoferrin |
Biological Components

Amino Acid Content
Whey is made up of a number of proteins including beta-lactoglobulin, alpha-lactalbumin, bovine serum albumin (BSA) and glycomacropeptide (GMP). Collectively, these contain a full spectrum of amino acids including the BCAAs leucine, isoleucine and valine. BCAAs are required for tissue growth and repair and leucine in particular plays a key role in the translation-initiation of protein synthesis. The sulphur-containing amino acids cysteine and methionine are also found in high concentrations in whey protein, contributing to enhanced immune function through intracellular conversion to glutathione. Interestingly, GMP – although a source of BCAAs – lacks the aromatic amino acids phenylalanine, tryptophan and tyrosine. This makes it a viable protein option for individuals with PKU (Phenylketonuria).

Lactoferrin
Lactoferrin is a non-haem iron-binding glycoprotein with antimicrobial and antioxidant effects. Comprising a single polypeptide chain with two binding sites for ferric ions, whey lactoferrin appears to exert its effects by regulating iron absorption.

Immunoglobulins
Immunoglobulins form a significant 10-15% of total whey proteins derived from bovine milk and of these, IgG has been found at concentrations of 0.6-0.9 mg/ml. According to the results of an in vitro study, bovine IgG at concentrations as low as 0.3mg/ml suppressed synthesis of human IgG, IgA and IgM by up to 98%. Based on these findings, the study concluded that bovine milk has the potential to modulate immune response in humans. Other studies have demonstrated that raw milk from non-immunised cows contains specific antibodies to E. coli, Salmonella enteriditis, S. typhimurium, Shigella flexneri and human rotovirus.

Lactoperoxidase
Lactoperoxidase is the most abundant enzyme in whey and has been shown to have anti-bacterial effects across a range of species. Its effects are linked to its ability to reduce hydrogen peroxide, catalysing peroxidation of thiocyanate and certain halides (including iodine and bromium). Lactoperoxidase appears to have the qualities of a stable preservative as it is not inactivated during the pasteurisation process.

Mechanism of Action
Whey’s antioxidant and detoxifying activity is most likely linked to its contribution to the synthesis of glutathione (GSH). Cysteine (which contains an antioxidant thiol group) combines with glycine and glutamate to form GSH. GSH is the major endogenous antioxidant produced by cells, providing protection for RNA, DNA and proteins via its redox cycling from GSH (the reduced form) to GSSH (the oxidised form). Through direct conjugation, GSH detoxifies a host of both endogenous and exogenous toxins including toxic metals, petroleum distillates, lipid peroxides, bilirubin and prostaglandins.

Lactoferrin’s antioxidant and antimicrobial effects have already been touched on briefly. Due to its ability to chelate iron, organisms requiring this metal to replicate would seem to be particularly vulnerable to lactoferrin’s effects. Lactoferrin also demonstrates an ability to stimulate immune responses involving natural killer (NK) cells, neutrophils and macrophage cytotoxicity. Furthermore, a mouse study concluded that lactoferrin acts as an anti-inflammatory by regulating levels of tumour necrosis factor (TNF) and interleukin 6 (IL-6).

The protein beta-lactoglobulin contains anti-hypertensive peptides which act as significant angiotensin 1 converting enzyme (ACE) inhibitors. Cholesterol-lowering effects have also been noted as a result of changes in micellar cholesterol solubility in the intestine.
Absorption
Whey proteins are considered to be ‘fast proteins’ in that they reach the jejunum quickly after entering the gastrointestinal tract. Once in the small intestine (SI), whey undergoes slow hydrolysis which encourages greater absorption over the length of the SI. This superior absorption makes whey an ideal optional source of vital protein for those with compromised GI function, such as ileostomy patients. It is speculated that cancer patients undergoing chemotherapy may also benefit, as anti-cancer therapies influence nutrient intake and absorption.

Clinical Indications
Cancer
A number of animal studies have examined whey’s anticancer potential, believed to derive largely from the antioxidant, detoxifying and immune enhancing effects of GSH and lactoferrin. In the presence of lactoferrin, colon cancer induced in rats showed reduced tumour expression while metastasis of primary tumours in mice was inhibited. Results of an in vitro study have also been encouraging, demonstrating inhibition of growth in human breast cancer cells when treated with the protein BSA.

A small number of clinical trials have been undertaken, proposing that high levels of GSH in tumour cells confer resistance to chemotherapeutic agents. Of these, one study of 5 patients produced conflicting results, highlighting the need for larger trials. In another, 20 patients with stage IV malignancies were treated daily with 40g whey in combination with supplements such as ascorbic acid and a multi-vitamin/mineral formulation. Six months later the 16 survivors demonstrated increased levels of NK cell function, GSH, haemoglobin and haematocrit. Unfortunately the study did not include a comparison with whey alone.

Whey may also have a role to play as part of an integrated approach which combines nutrition, exercise and hormonal support to counteract the muscle-wasting frequently associated with cancer. Professor Vickie Baracos explores the feasibility of using this sports medicine model in her article ‘New Approaches in Reversing Cancer-related Weight Loss’.

Hepatitis B
Although an initial in vitro study found that bovine lactoferrin prevented hepatitis C virus (HCV) in a human hepatocyte line, subsequent trials have proved inconclusive. However, results for hepatitis B virus (HBV) have been more positive, particularly an open study on 8 patients taking 12g of whey daily. Subjects demonstrated improved liver function markers, decreased serum lipid peroxidase levels and increased IL-2 and NK activity.

Human Immunodeficiency Virus (HIV)
Individuals with HIV commonly have low levels of GSH. Several studies have sought to address this by testing the effect of whey protein on the GSH levels of HIV-positive subjects. In one instance, 18 participants were randomised to receive daily doses of 45g whey protein from two different products over a six month period. Only one of the products significantly elevated GSH levels (Protectamin®, manufactured by Fresenius Kabi, Germany), a result that may be related to production at differing isolation temperatures and non-comparable amino acid profiles.

Cardiovascular Disease
According to the results of a number of studies, milk intake and milk products can lower blood pressure and reduce the risk of hypertension. In one particular eight week trial, 20 healthy men were
given a combination of fermented milk and whey protein concentrate to establish whether serum lipids and blood pressure would be affected. The placebo group received only unfermented milk. After eight weeks, the fermented milk group demonstrated comparatively higher HDLs, lower triglycerides and reduced systolic blood pressure. The effect of whey alone was not studied.

**Osteoporosis**
Milk basic protein (MBP) is a component of whey which demonstrates the ability to not only suppress bone resorption, but also to stimulate proliferation and differentiation of osteoblastic cells. MBP contains largely lactoferrin and lactoperoxidase. Animal studies suggest that lactoferrin may be the key active component, mediating its effects through two main pathways: LRP1 (a low-density lipoprotein receptor-related protein which endocytoses lactoferrin into the cytoplasm of primary osteoblasts) and p42/44 MAPK (which stimulates osteoblast activity). A number of clinical trials support MBP’s positive effects in both men and women, the latter ranging in age from young to post-menopausal. Daily doses of MBP 40mg (equivalent to 400-800 mL of milk) appear to be sufficient to produce significantly increased bone mineral density and reduced bone resorption.

**Stress Adaptation**
Whey enriched with the protein alpha-lactalbumin has been shown to improve cognitive performance and mood in stress-vulnerable subjects. Alpha-lactalbumin is particularly high in tryptophan and the authors propose that this acts as a substrate to increase serotonin levels which may be vulnerable to depletion by chronic stress. After the studies, subjects all showed higher ratios of plasma Trp-LNAA (the ratio of plasma tryptophan to the sum of the other large neutral amino acids), believed to be an indirect indication of brain serotonin function.

**Gastrointestinal Support**
Whey is used as a gastrointestinal supporter by health professions such as Nutritional Therapy Practitioners. Its mucosa-protective effects are well-proven by several animal studies and are likely to be associated with its GSH-stimulating properties. In addition to its role in GSH synthesis, the amino acid glutamate may play a further role when it is converted to glutamine, an amino acid utilised as a fuel by intestinal mucosa.

**Choosing the Right Whey Product**
Given the variety of different whey products available, it is possible to select products for specific clinical indications. For athletes or those looking for a highly-absorbable, low allergenicity protein source, hydrolysed whey – with its readily available di- and tri-peptides - may be a good option. For the immune-compromised or microbe-challenged, undenatured whey’s high levels of lactoferrin and immunoglobulins may be helpful.

**Comparison of Whey with Pea and Soy Protein Powders**
Despite no serious adverse reactions to whey powders having been reported, they may not be suitable for those with frank milk allergies. That said, it is worth noting that casein – which is not a component of whey - is often the culprit for dairy-sensitive individuals. Although most whey proteins are processed to remove all but trace amounts of lactose, for the lactose-intolerant, a de-lactosed whey may be a more sensible option. Prior to using therapeutic quantities, a challenge test with a small amount of the proposed whey product would certainly be advisable for those with dairy sensitivities.

Non-dairy protein powders are an alternative for individuals with dairy issues, including vegans. Table 2 below compares the amino acid profile of specific whey, pea and soy protein powders and highlights possible clinical indications for each.

<table>
<thead>
<tr>
<th>Amino Acids</th>
<th>Whey</th>
<th>Pea</th>
<th>Soy</th>
</tr>
</thead>
</table>

Table 2: Comparison of Whey, Pea and Soy Protein Powders
<table>
<thead>
<tr>
<th>(*=Essential)</th>
<th>(Metagenics ‘Perfect Protein’ – micro-filtered isolate) g/100g</th>
<th>(Kirkman Pea Protein Powder) g/100g</th>
<th>(NutraBio Soy Protein Isolate) g/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>4.00</td>
<td>5.04</td>
<td>3.80</td>
</tr>
<tr>
<td>Arginine</td>
<td>1.43</td>
<td>8.71</td>
<td>6.70</td>
</tr>
<tr>
<td>Aspartic Acid</td>
<td>8.78</td>
<td>12.43</td>
<td>10.20</td>
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<tr>
<td>Cysteine</td>
<td>1.83</td>
<td>0.76</td>
<td>1.10</td>
</tr>
<tr>
<td>Glutamic Acid</td>
<td>13.57</td>
<td>13.74</td>
<td>16.80</td>
</tr>
<tr>
<td>Glycine</td>
<td>1.43</td>
<td>4.64</td>
<td>3.70</td>
</tr>
<tr>
<td>Histidine</td>
<td>1.30</td>
<td>2.52</td>
<td>2.30</td>
</tr>
<tr>
<td>Isoleucine (BCAA)*</td>
<td>4.70</td>
<td>5.59</td>
<td>4.30</td>
</tr>
<tr>
<td>Leucine (BCAA)*</td>
<td>8.09</td>
<td>8.44</td>
<td>7.20</td>
</tr>
<tr>
<td>Lysine*</td>
<td>6.87</td>
<td>6.82</td>
<td>5.60</td>
</tr>
<tr>
<td>Methionine*</td>
<td>1.74</td>
<td>1.31</td>
<td>1.10</td>
</tr>
<tr>
<td>Phenylalanine*</td>
<td>2.30</td>
<td>6.13</td>
<td>4.60</td>
</tr>
<tr>
<td>Proline</td>
<td>4.26</td>
<td>5.29</td>
<td>4.50</td>
</tr>
<tr>
<td>Serine</td>
<td>3.52</td>
<td>4.80</td>
<td>4.60</td>
</tr>
<tr>
<td>Threonine*</td>
<td>5.35</td>
<td>4.34</td>
<td>3.30</td>
</tr>
<tr>
<td>Tryptophan*</td>
<td>1.43</td>
<td>1.06</td>
<td>1.20</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>2.35</td>
<td>3.12</td>
<td>3.30</td>
</tr>
<tr>
<td>Valine (BCAA)*</td>
<td>4.48</td>
<td>5.27</td>
<td>4.40</td>
</tr>
</tbody>
</table>

A comprehensive functional food which supplies key proteins such as lactoferrin and immunoglobulins in addition to amino acids. Ideal for vegetarians and/or individuals with sensitivity issues. Suitable for vegetarians and those with sensitivity issues, although soy may be a problem for some. A source of isoflavones which may have possible positive effects on heart disease, menopausal symptoms, osteoporosis and breast/prostate cancers.

**Conclusion**

Whey protein is a complex functional food which reflects its wide range of potential therapeutic applications. The variety of available products allows for a tailored clinical approach although caution is advised if dairy sensitivity is suspected. In these cases, non-dairy options such as pea or soy protein powders may be viable alternatives.

**About the Author**

Carol Murrell is a qualified nutritional therapist who trained at the Centre for Nutrition & Lifestyle Management (CNELM) in Wokingham. A keen runner and cyclist, her areas of special interest include sports nutrition from a nutritional therapy perspective, women’s health and cancer care. She is also a qualified NLP (Neuro Linguistic Programming) practitioner and uses these powerful techniques to help individuals effect change in their lives. Carol is a Professional Member of the South African Association of Nutritional
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