

# **A Brief Overview of Whey and Colostrum and Their Potential as Functional Food Ingredients**

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“Let food be thy medicine and medicine be thy food.” -*Hippocrates*

“Clearly, dietetics professionals can no longer evaluate foods solely in terms of macro- and micro-nutrient content. Consideration of other physiologically active components ...will be necessary... In the future, a wide range of select foods may be “prescribed” to enhance the health of an individual. This is a shift from our earlier employed nutrition education approach that focused on limiting intake of foods high in “unhealthful” components such as fat and cholesterol.”

-*American Dietetic Association, [www.eatright.org](http://www.eatright.org)*

“Phytonutrients (fi'to-noo'-tree nts) are health promoting compounds found in plants. Zoonutrients (zoh-uh-noo'-tree-uh nts) are health promoting compounds found in animals... that provide health benefits beyond the provision of essential nutrients and energy. Functional foods are those that contain one or more of such substances...thought to influence health.”

-*Diet and Health Trends Concepts and Controversies, University of Idaho*  
<http://www.avs.uidaho.edu/avs305/Intro%20to%20nutrients.ppt>

“Understanding how molecular structures have evolved to provide nutritional functions in animals will lead to a new generation of foods that can deliver on the promise of maintaining optimal health.”

-*Robert E. Ward and J. Bruce, Zoonutrients and Health, Food Technology, Vol 57, March 03, pp 30- 36*

“An ounce of prevention is worth a pound of cure.”-*Benjamin Franklin, Poor Richard's Almanac*

## Functional Foods from Plants *and* Animals

We have long known that foods contain the nutrients we need to sustain life. Nonetheless, nutrition and food scientists are continually finding new beneficial components in food that help keep us healthy and prevent the development of disease states. Indeed, the very concept of what benefits foods can provide is continuously evolving. The previous emphasis on health maintenance through recommended nutrient allowances and dietary guidelines has recently evolved into a focus on the promising use of foods to promote optimal health and reduce the risk of chronic diseases.<sup>1</sup> Today, nutritionists describe foods that are rich in certain “ingredients” that may provide a health benefit beyond the traditional nutrients it contains as *functional foods*.<sup>2</sup> These functional food ingredients are sometimes described as “quasi-nutrients” and are best exemplified by two main groups, the *phytonutrients* and the *zoonutrients*.

### The Phytonutrients

A significant direction in the effort to understand the health benefits of plant foods as the basis for the creation of functional foods is the characterization of their physiologically active constituents called *phytonutrients*. It has long been appreciated that food plants contain significant levels of low molecular weight, secondary metabolites with important roles for plant protection.<sup>3</sup> Only more recently has their role in optimizing human health been appreciated.<sup>4</sup>

For example, phytonutrients have been demonstrated to provide the following physiological effects:

- facilitate cell-to-cell communication,<sup>5</sup>
- modify cellular receptor uptake of hormones,<sup>6</sup>
- convert to vitamin A,<sup>7</sup>
- repair DNA damage from toxic exposure,<sup>8</sup>
- detoxify carcinogens through the activation of the cytochrome P450 and Phase II liver enzyme systems,<sup>9</sup>
- serve as antioxidants to help prevent various forms of cancer,<sup>10</sup>
- cause apoptosis (cell death) in cancer cells,<sup>11</sup>
- enhance immune response,<sup>12</sup>
- help prevent cardiovascular disease,<sup>13</sup>
- help prevent osteoporosis,<sup>14</sup>
- help prevent macular degeneration and cataracts.<sup>15</sup>

### The Zoonutrients

Just as plant foods may provide phytonutrients, animal foods may also contain beneficial substances called *zoonutrients*. Zoonutrients are food molecules that have been shown to have potential in modifying multiple physiological functions including anti-inflammatory, anti-hypertension and antimicrobial actions, stimulation of beneficial bacteria, the maturation of intestinal cells, and the education of the immune system.<sup>16</sup>

The currently more familiar anti-inflammatory, anti-clotting and triglyceride lowering effects of the omega-3 oils of cold water fish are largely an attribution of their zoonutrients EPA and DHA.

In Chicago Oct., 1997, the International Whey Conference reported the following seven findings concerning the zoonutrients in whey:

1. Very low molecular-weight whey peptides may help prevent cancer and heart disease.
2. Certain whey peptides boost immune status by increasing the body’s main cellular protector, glutathione.
3. Whey protein, by increasing thymus development, has reduced colon cancer in rats.
4. One powdered whey supplement in conjunction with photodynamic therapy reduced tumor size by 60% in rats.

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5. Certain whey peptides may aid dieting by dramatically increasing the release of cholecystokinin (CCK), an appetite suppressant.
6. Three whey peptides (lactoferrin, lactoperoxidase and immunoglobulin) act as antibacterial preservatives and free radical scavengers.
7. Whey contains growth factors (IGF-I and II) proven to assist in gut and wound healing, inside and out.  
(Note: colostrum is even more powerful in this aspect.)

The focus of this paper will be to first briefly examine the protein and peptide zoonutrients in whey and colostrum, and then examine some ingredients that might work synergistically in a dairy based, zoonutrient rich, functional food formula.

## Whey Protein

Whey proteins from dairy are not something new. They have been available for hundreds of years, though mostly they were considered as more or less a waste product of cheese production! It has only been during the last 25 years that new processing methods and scientific research have unlocked the true potential of whey proteins.

***New preliminary research suggests whey protein may be able to reduce stress and depression by lowering cortisol and increasing brain serotonin, improve liver function in hepatitis, help chronic fatigue, improve athletic performance, and reduce blood pressure.***

Today, whey protein is often described as a “nutritionally perfect protein” in the sense that it contains all the essential and non-essential amino acids required by the human body. Whey’s amino acid profile is closely related to the optimal physiological needs of the human body, including an abundance of sulfur-containing amino acids, all in a highly bio-available form. Whey protein’s quality is variously described by such terms as high *Biological Value* (BV), high *Protein Efficiency Rating*, (PER), and high *Net Protein Utilization* (NPU). Human breast milk is 80% whey protein!

As whey proteins are so easily digested and well utilized they may be an ideal source of protein and essential amino acids for those ill and elderly with declining appetites, challenges with food preparation, less than optimal dentition and/or digestive strength. Being low in carbohydrates and high in protein, whey protein is well suited for restricted carbohydrate diet strategies.

In addition, whey protein may be the best candidate for maximizing muscle growth. Whey protein contains an optimal balance of amino acids for muscle growth, especially *glutamine* or *glutamic acid*, and *taurine*. L-Glutamine is the most abundant non-essential free amino acid in the body. The concentration of free glutamine appears to influence whether muscle will break down due to low glutamine content or build up via high glutamine content. Athletes suffering from overtraining syndrome seem to have decreased blood concentrations of glutamine. This may lead in turn to suppression of immune functions and slow recovery time following exercise. Even patients recovering from trauma (surgery, burns, stress, chemotherapy, radiation etc.) have an increased demand for glutamine. Such increased demand is probably the result of increased use of glutamine by the immune, antioxidant, and detoxification systems and the decreased integrity of various injured or irradiated tissues.

Whey protein’s amino acid profile also features the highest percentages of *branched-chain amino acids* (BCAA). Diets high in BCAA demonstrate less muscle loss when the body muscle is being broken down as it is in severe infections, surgery, burns, calorie restriction, and strenuous exercise. This muscle and lean body mass sparing effect occurs because BCAA serve as a direct energy source thereby lessening muscle breakdown for energy. Indeed, whey protein blends have quickly become the protein of choice among competitive bodybuilders.

Undenatured whey protein is rich in *cystine*, the thermo-labile amino acid which represents an effective *cysteine* delivery system for the cellular synthesis of glutathione. Both cysteine and glutamine, along with glycine, are necessary the synthesis of the tri-peptide *glutathione* (GSH), one of the major detoxifiers (Phase II sulfonation) and antioxidants of the body. Enhancing glutathione levels also helps reduce the risk of infections by improving white blood cell functions. However, the unique disulfide cystine bonds of whey are heat sensitive (thermo-labile) so only carefully processed, *undenatured* whey proteins deliver bioavailable cystine di-peptides for intracellular conversion to cysteine, thus maximizing glutathione levels with its important immune, antioxidant, and detoxification benefits.<sup>17</sup>

New preliminary research suggests whey protein may be able to reduce stress and depression by lowering cortisol and increasing brain serotonin, improve liver function in hepatitis, help chronic fatigue, improve athletic performance and reduce blood pressure.<sup>18</sup> Other reports show whey proteins have recently been shown to have positive impact potential in appetite suppression, cholesterol reduction, and the inhibition of dental plaque and dental caries.<sup>19</sup> Researchers at the [Arkansas Children’s Nutrition Center](#), funded by the USDA, have found that whey and soy protein may help prevent breast cancer.<sup>20</sup>

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## The Sub-Fractions of Whey Protein

The proteins in whey come in many protein sub-fractions, namely *Beta-lactoglobulin*, *Alpha-lactalbumin*, *Immunoglobulins(Ig)*, *Bovine Serum Albumin (BSA)*, *Glycomacropeptide (GMP)*, *Lactoferrin*, *Lactoperoxidase*, and *Lysozyme*. Their relative amounts will vary somewhat, especially depending on how the whey proteins are processed.

*Beta-lactoglobulin* is the most abundant whey protein component, making up approximately 50-75% of the whey protein. It binds fat-soluble vitamins making them more available to the body. It is rich in muscle sparing energy supplying branched chain amino acids (BCAAs).

*Alpha-lactalbumin* is the second most abundant whey protein component, making up approximately 12-24% of the whey protein. It is primary protein found in human breast milk. Being high in tryptophan, an essential amino acid, potential benefits include sleep regulation and mood improvement under stress. Alpha-lactalbumin is the only whey protein component capable of binding calcium.

*Immunoglobulins* (mostly IgG, with IgA and IgM), and *Bovine Serum Albumin (BSA)*, make up approximately 5-15% of the whey protein. Immunoglobulins and BSA, the latter a particularly cystine rich sub fraction, are the predominant whey protein components found in colostrum. Immunoglobulins convey passive immunity, especially enterically.

*Lactoferrin*, a glyco-protein, makes up approximately .2 -1% of the whey protein. Lactoferrin inhibits the growth of bacteria and fungi due to its ability to bind iron, a function known as *ferro-privation*.<sup>21</sup> Iron is a nutrient usually required for bacterial growth. Lactoferrin also promotes the growth of beneficial bacteria such as *L. Bifidus*, helping infants establish good microbial conditions in their intestines, described as “*eubiosis*”. It is also an antioxidant that naturally occurs in many body secretions such as tears, blood, breast milk, saliva and mucus.<sup>22</sup> Lactoferrin has anti-viral, anti-tumor activity, anti-inflammatory / anti-oxidant activity, and immuno-modulating activity.<sup>23, 24, 25, 26, 27</sup> Lactoferrin is also a cystine rich sub fraction.

*Lactoperoxidase* makes up approximately 0.5% of the whey protein. Like lactoferrin, it inhibits the growth of iron dependent bacteria.

*Lysozyme* makes up less than 0.1% of the whey protein. Lysozyme contains immunity enhancing properties.

*Glycomacropeptide (GMP)* helps control appetite and inhibit the formation of dental plaque and dental cavities. Levels may range from 1% to 18%, depending on how the whey is processed.

## Weighing the Different Forms of Whey

*Whey Protein Concentrates (WPC)* may supply up to 80% protein and usually include medium to comparatively high lactose levels. *Whey Protein Isolates (WPI)* and *Whey Protein Hydrosylates (WPH)* contain little to no appreciable lactose or carbohydrates, are less than 1% fat, and are usually 90% or more protein!

The advantage of whey protein isolate (WPI) is that it is highest in protein and lowest in lactose. However, some immune peptides, GMP, vitamins and minerals are lost in an isolate. The advantage of a *hydrosolate (WPH)* is that it is highest in BCAA, being approximately 70% beta-lactoglobulin, and is therefore prized by some body builders. It is also almost “pre-digested” by the process of *hydrolysis*, making it even easier to digest. But the hydrolysis process also tends to *denature* the otherwise *bioactive* peptides in whey. *Whey protein concentrate (WPC)* is a more nutritionally whole and complete product, but per gram supplies less protein and more fat, cholesterol and lactose. Many people are intolerant of the latter. One solution for a dairy based functional food is to combine the low lactose, low fat, high protein of WPI with the concentrated *bioactive* peptides of whole colostrum.

As mentioned earlier, to have maximum efficacy as a functional food, it is most important that the whey peptides are not denatured during any of the above processing.<sup>28</sup> We will examine “denaturization” more fully shortly. Furthermore, some health professionals prefer whey products from cows not given growth hormones, routine prophylactic antibiotics, or GMO or pesticide containing feeds.

## The Whey to Weight Loss

Our present understanding of the physiology of appetite is still incomplete. However, we are aware that there are various *endogenous brain messenger substances* (neuro-transmitters, neuro-hormones) that effect, among other things, mood, memory, relaxation, focus, and appetite. A better appreciation of the relationship of these brain messenger chemicals to their nutritional building blocks, particularly the amino acids, may well be an important factor in endeavors to modulate appetite and thereby facilitate clinical efforts to attain and maintain optimal lean body mass.

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According to Julia Ross, M.D. in her book “The Diet Cure”, published in 2000, one such brain messenger is *serotonin*, which is known to affect mood, promote a relaxed feeling of “lightness”, support deep sleep and melatonin production, and affect appetite cravings, especially for carbohydrates.

The amino acid “building block” to serotonin is *tryptophan*. It is therefore important to appreciate that the ratio of tryptophan to *large neutral amino acids* and *branched chain amino acids* determines tryptophan’s availability to the brain. The large neutral amino acids (LNNA) are *tyrosine* and *phenylalanine*, and the branched chain amino acids (BCAA) are *leucine*, *isoleucine*, and *valine*, all of which compete with tryptophan to crossing the protective blood brain barrier to enter the brain.<sup>29</sup>

Furthermore, it is important to be aware that *insulin*, which is released as the result of ingesting carbohydrates, as any serious body builder knows, is *anabolic*, meaning growth promoting. Insulin facilitates the removal of proteins, specifically the aromatic and branched chain amino acids, from the bloodstream to be largely directed to muscle tissue. This function of insulin helps remove these competitors to tryptophan’s crossing the blood brain barrier. *Insulin resistance* would interfere with this function.

In a 2003 paper reported in the American Journal of Clinical Nutrition<sup>30</sup>, both the absolute plasma tryptophan concentration and the ratio of tryptophan to large neutral amino acids were low. This was true both *during* and *after* the successful weight loss programs, even though said programs were successful in maintaining lean body mass. The authors also noted that the obese participants are often insulin resistant as well. Such diminished insulin activity may be an aggravating factor in continued low plasma ratios of large neutral amino acids to tryptophan levels. Absolute plasma concentrations of tryptophan as such were also reported to be low in dieting patients *before* successful weight loss. According to the authors, Breum et al., these two observations, and their potential concomitant effects on mood and appetite, may well be part of the reasons for *relapse* after diet induced weight loss!

These data strongly support the notion that obese persons may do well to be supplementing tryptophan. As both low levels of tryptophan and its availability to the brain vis-à-vis tryptophan/LNAA ratios tend to lead to below optimal serotonin levels, which is subsequently conducive to carbohydrate cravings, poor sleep, low self esteem and mood, and impulsive behavior, such a notion is not without logical argument.

Unfortunately, the FDA continues to argue what many feel is its unjustified prohibition of tryptophan as a dietary supplement. An alternative, and perhaps even superior, approach may be to utilize high quality whey protein isolates. WPI has both an unusually rich supply of tryptophan and a higher ratio of tryptophan to BCAAs as compared to other proteins such as soy protein or casein. The simultaneous ingestion of as little of 10 gm of carbohydrate may initiate the release of insulin, with its potential salubrious effect on tryptophan uptake by the brain and the brain’s neurophysiology.

As WPI is 90% or more highly biologically available and complete protein, with minimal additional calories from carbohydrates and fats, it may be in itself one of the more ideal food choices to include in weight loss and lean body mass maintenance nutrition strategies. Based on the above understandings, it may well be best to ingest whey proteins without competition from other protein sources, and with some small amount of carbohydrate, like a few ounces of fruit juice or a teaspoon of molasses, rich in chromium, potassium and magnesium. Additionally, it may be best to not slow down the assimilation of the amino acids with simultaneous ingestion of large amounts of fiber or fats, if our desire is to generate a more immediate effect on mood, sleep, behavior, and appetite.

## **Health Enhancing Potential of Udenatured Whey Protein Zoonutrients**

As we have pointed out previously, whey protein is not only a great source of high quality protein macro-nutrition, rich in complete, balanced, easily absorbed amino acids, it is also a rich source of a multitude of unique *zoonutrients* (zoh-uh-noo’-tree-uh nts).

As *phytonutrients*, like lycopene, lutein, phytoestrogens and polyphenols, are non-nutritive phyto-chemicals in plant foods that nonetheless have salubrious metabolic effects in the animals and humans who consume them, even so *zoonutrients* are similarly efficacious animal sourced quasi-nutrients that may help in optimizing physiological status and homeostasis in the animals and humans who consume them. In 2003, Ward and Bruce write in Food Technology, “...different peptides from milk have been well described to modify blood pressure, neurologic activity, immune functions, food intake, intestinal functions, and even dental calcification... These discoveries have prompted scientists to pursue...how specific molecules in foods affect health, how foods modulate the immune system and the interaction between beneficial bacteria, pathogenic bacteria, and our innate and acquired immune-protective mechanisms.”<sup>31</sup>

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JB German of UC Davis Dept. of Food Science and Technology writes, “Metabolic products of the lactating mammary gland (milk) are being shown to provide a spectrum of benefits... Research to explore the majority of benefits of non-essential nutrients was accelerated when investigators began to explore the principles of immunology and physiology in molecular detail using isolated cells, and to assemble screening assays... Surprisingly, components from milk were discovered to exert significant effects on many of these assay systems. This led to the second generation of zoo-nutrients, molecules that modified physiological targets of known health problems including anti-inflammatory, anti-hypertension and antimicrobial actions. Now modern biological tools are... deducing dietary functions that were previously unknown, including as examples, the stimulation of beneficial bacteria, the maturation of intestinal cells and the education of the immune system...(that) will provide the next generation of health properties.”<sup>32</sup>

However, it is very important to note that the various zoonutrients in milk are more or less “thermo-sensitive” meaning that they are easily deformed or “denatured” by heat, as the following quotes will demonstrate.

“Recent observations have revealed to us that the described biological activity of the whey protein concentrate, already shown to be unrelated to its nutritional quality (i.e., related to the zoonutrients), is actually dependent on the undenatured conformation of the proteins...The immuno-enhancing and the other specific biological properties of dietary whey protein...are heat labile and dependant upon the undenatured (native) state of the protein... and are independent of its nutritional quality which is unaltered by the process of denaturation...Our data indicate that the humoral immune response is highest in...a dietary whey protein concentrate exhibiting the highest solubility (undenatured conformation)...this type of whey protein concentrate exhibit(s) higher levels of tissue glutathione (the major endogenous antioxidant and major detoxicant in humans). The presence in the serum albumin fraction of glutamyl-cysteine groups (rare in food protein) and the specific intramolecular bond as related to the undenatured conformation of the molecule are considered to be key factors in the glutathione-promoting activity of the (whey) protein mixture.”<sup>33</sup>

“Milk whey protein fed to mice as a constituent of the diet elicited a systemic humoral response.... The serum antibodies were of the IgG class (Immunoglobulin G)... However, when heat-denatured whey protein was fed, the animals showed only a poor serum response...”<sup>34</sup>

“Comparison of IgG content in raw milks and corresponding HTST (High Temperature Short Time)-pasteurized milks of varying fat content indicated 59–76% retention after pasteurization, (or 24% to 31 % loss!- editor)...This study demonstrates the dependence of bovine IgG stability in milk products on severity of thermal treatment used in various commercial processes.”<sup>35</sup>

“The kinetic and thermodynamic parameters for heat induced denaturation of IgG in colostrum ... should be taken into account in the design of heat treatments of milk in order to preserve the biological function of Ig.”<sup>36</sup>

“The efficacy of...oral administration of Ig from colostrum...provides effective protection against...(bacterial) infections of human infants and adults... (and) several serotypes of rotavirus (that) prevents the occurrence of diarrhea and reduces the duration of agent excretion in infants...To preserve the immunological function of Ig, the effects of processing and storage conditions on stability must be known. ... the ability of (heated) IgG to bind the antigen and, thus, to maintain its immunological activity probably has been overestimated until now. In conclusion, these considerations should be taken into account in the design of heat treatment of milk in order to preserve the biological function of Ig...”<sup>37</sup>

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In conclusion, it is most important when considering “which whey to go” that if one wants to maximize the potential benefits of the zoonutrients in a whey protein formula, that one chooses a product that is processed with minimal heat exposure and can demonstrate that all the whey products in the blend are highly undenatured.

#### Colostrum: Nature’s Most Nutrient Dense Zoonutrient

“many hormones, growth factors and bioactive substances present in the maternal organism are present in colostrum..., often exceeding concentrations that occur in maternal plasma” -Endocrinology Review, 1993<sup>38</sup>

“...colostrum has been used to successfully treat: Thrombocytopenia, Anemia, Neutropenia, Myasthenia Gravis, Guillain Barre Syndrome, Multiple Sclerosis, Systemic Lupus, Rheumatoid Arthritis, Bullous Pamphigoid, Kawasaki’s Syndrome, Chronic Fatigue Syndrome and Crohn’s disease, among others.” -Dr. Dwyer; NEJM<sup>39</sup>

**“... different peptides from milk have been well described to modify blood pressure, neurologic activity, immune functions, food intake, intestinal functions, and even dental calcification...”**

Although whey protein can be rich in zoonutrients when properly processed, colostrum is nature's most nutrient dense zoonutrient. Robert Preston, MD, President of the International Institute of Nutritional Research, defines colostrum in the following manner: "*When a (mam-mal)... gives birth to its offspring, its mammary glands filter out of the blood the immune factors it has acquired through a lifetime of fighting disease-causing organisms. It then concentrates these factors into special non-milk immune supporting fluid called colostrum. A mother animal produces true colostrum for only the first twenty-four hours after giving birth.*"<sup>40</sup>

Indeed, besides being very rich in highly bioavailable vitamins and minerals, the colostrum of mammals produced has two main functions: to supply both passive and active *immune factors* for the otherwise highly susceptible new born, and provide *growth factors*, not only to the immune system via the thymus, but for cells throughout the body.

#### Colostrum's Immune Factors

*Immunoglobulins*: Immunoglobulins are protein molecules that provide passive immunity effects that can be efficacious, both prophylactically and therapeutically, against allergens, bacteria (including *H. pylori*), viruses, parasites, fungi and yeast. The immunoglobulins present in colostrum are predominantly IgA with trace amounts of IgD, IgE, IgG, and IgM. Human colostrum typically contains 2% IgG content, while whole bovine colostrum can have from 8% to 20% IgG. Processing concentration techniques can yield as high as 40% colostrum, though such would no longer be a "whole" colostrum product, and some other peptides and factors are thereby diminished. Immunoglobulin concentrations should be verified by high performance liquid chromatography (HPLC) to verify label claim.

*Lactalbumin*: These protein molecules are rich in double-bonded cystine which promotes the production of glutathione, the major intracellular endogenous antioxidant and detoxicant. Lactalbumin may also help raise serotonin in deficiency states and lower cortisol when in excess.

*Lactoferrin*: Discussed earlier, lactoferrin is most familiar as an iron-binding protein. Lactoferrin's competition for available iron in the gut both inhibits bacterial and viral populations and oxidation, and the resulting "down stream" inflammation, from excess iron radicals.

*Lysozymes*: Lysozymes contain enzymes that can attach to and digest bacteria cell walls, thus destroying them.

*Glycoproteins*: These sugar-amino complexes act as protease and trypsin inhibitors, thus protecting the immune and growth factors in colostrum which are otherwise vulnerable to degradation via enzymatic action.

*Proline-rich Polypeptides (PRP)*: These are small, very low weight molecules (6,000 Daltons) that have an active immune modulating effect upon the thymus. They have been variously described as "biological response modulators", "info-peptides", "transfer factors" and "colostrinin"<sup>41,42</sup>. Immunodeficiency (Th1 deficit states), as in HIV, EBV and herpes, may be thus counteracted, while immune hyperactivity (Th2 hyperactivity), as in autoimmune and allergic diathesis conditions, may be inhibited.<sup>43</sup> PRPs isolated from colostrum and taken sublingually have shown great promise as an immune equilibrating nutraceutical and as a potential therapy for Alzheimer's disease!<sup>44</sup>

The concentration of these most bioactive peptides, the proline rich polypeptides (PRPs), in whole colostrum powder is usually between 1-3% of the total powder weight. However, most manufacturers of colostrum powders remove much of the PRP fraction, along with lactose, minerals and water, using ultra-filtration technology, to elevate the *passive immunity* supporting immune globulins and the protein content of the powder. This then reduces the *active immunity modulation* effectiveness of the colostrum powder. Patented technologies now exist that can fortify whole colostrum such that it provides 6% PRPs by weight!

*Cytokines*: Cytokines are integral to intercellular communications that regulate immune activity and related down stream inflammatory responses. These immune messengers include the *interleukins*, the *lymphokines*, and *interferon*. The PRP's mentioned above have a modulating effect on the cytokines.

#### Colostrum's Growth Factors

Growth factors from mammalian bovine colostrum are by and large not species specific. Indeed, they are almost identical to human colostrum! The various growth factors in whole colostrum are by definition *anabolic*, stimulating both generation and regeneration of *epithelial*, *mesenchymal*, and *endothelial* cells. During periods of low calorie intake, growth factors favor the use of fat for fuel and are therefore protein and "lean body mass" sparing.

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*Insulin-like Growth Factor I and II:* Often abbreviated as IGF-I / IGF-II, these are the predominant growth factors in colostrum. They help regulate lipid, protein and carbohydrate anabolism. Of note, IGF-I is one of a handful of molecules that promotes the growth and repair of DNA and RNA.

*Epithelial Growth Factor:* EGF enhances dermal anabolism. Indeed, topical applications of EGF concentrates may soon be a common cosmeceuticals ingredient. Colostrum as such already is.

*Transforming Growth Factors A & B:* TGF A & B promote mesenchymal cellular proliferation. TGF thus has potential for assisting bone and cartilage repair, deep wound healing, and restoring intestinal integrity in “leaky gut” syndromes.

*Platelet-Derived Growth Factor:* PDGF promotes growth not only in connective tissue such as fibroblasts and smooth muscle, but has some promise in sparing and regenerating nerve tissue as well.

### Quality Considerations

As with most nutraceuticals, quality, and therefore clinical efficacy, greatly varies. According to Andrew Keech, PhD, of Advanced Protein Systems, some things to look for when choosing a colostrum product include:

- HPLC Analysis: Make sure there is High Performance Liquid Chromatography (HPLC) analysis on every batch to verify label claims for IgG percent.
- Low Heat Processing: Avoid high heat pasteurization, flash pasteurization without immediate cooling to 40 degrees F, and direct drying processes which all denature colostrum’s peptides.
- First and Second Milkings: The first and second milkings, taken within the first 24 hours of calving, are the richest in IgG and protein peptides. The best products use only these early milkings.
- Antibiotic/Hormone “Free”: The most desirable colostrum is from cows not routinely treated with prophylactic antibiotics or given synthetic growth hormones.
- Solubility: Clients and patients will prefer a colostrum powder that dissolves quickly without clumping.
- Freshness: When possible, prefer colostrum for cows whose climate conditions allow year-round production. Know that most colostrum is produced only once a year because calving typically occurs in the spring. As always, prefer manufacturers that follow “Good Manufacturing Practices” (GMPs). This should include a microbiological analysis on each product batch.
- Lactose digesting enzymes: Lactase may be added as to minimize lactose intolerance in susceptible persons.

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### Dosage

On a routine basis 2 gm per day is commonly suggested for purposes of daily prophylaxis. Therapeutic endeavors may approach 12 gm a day, spread out evenly over 3 or 4 dosings and for several weeks or months as necessary. Higher doses may need to take lactose intolerance into consideration. (Adding *lactase*, the lactose digesting enzyme, to the nutraceutical should prevent lactose intolerance symptoms.) Late evening

dosing may be too “energizing” for some persons. Colostrum should not be taken with protein digesting enzymes which may denature the peptides.

## The Physiological Functions of Proline Rich Polypeptides (PRP)

*Proline Rich Polypeptides* are perhaps the most powerful of colostrum peptides vis-à-vis *active* immune modulation and therefore deserve greater examination. Proline rich polypeptides are extremely small chains of 10 amino acids or less, notably proline, which nonetheless have a very powerful effect in initiating and balancing our immune responses.

Proline Rich Polypeptides, also known as PRP, enhance the ability of the thymus gland to release factors that help regulate immune functions in the body. Specifically, certain T cells, called *Th1 helper cells*, are antagonist to the activity of *Th2 helper cells* that promote certain functions of B lymphocytes. PRP can induce a shift from a predominantly *humeral* immune response to a more protective *cellular* response described as a “Th2 to Th1 shift”. Doing so may assist the immune system in more effectively fighting chronic viral and bacterial infections while simultaneously inhibiting the initiation of inappropriate inflammatory cascades associated with allergy, chemical sensitivity and auto-immune responses.

A more detailed review of some of the main physiological functions of proline rich polypeptides follows.

- Modulate the immune system - PRP promote T-lymphocyte function and can either stimulate the lymphocytes to become helper T-cells or suppressor T-cells.<sup>45,46,47</sup> Helper T-cells activate B-lymphocytes by presenting an antigen (such as a viral protein) to the B-cell, which then produces antibodies to that protein.<sup>48</sup> Helper T-cells also help produce memory T-cells which retain the “memory” of the antigen to shorten the response time in case of new infection.<sup>49</sup> Suppressor T-cells deactivate other lymphocytes, effectively turning off the immune response to avoid damage to healthy tissue.<sup>50</sup> PRP also stimulate the production of a whole range of cytokines, particularly the pro-inflammatory cytokines TNF-alpha and INF- gamma and the anti-inflammatory cytokines IL-6 and IL-10 .<sup>51,52</sup>
- Act as molecular signaling devices - PRP work through specific receptors on cell surfaces.<sup>53</sup>
- Stimulate undifferentiated lymphocytes in thymus to become either helper T-cells or suppressor T-cells - PRP from ovine (sheep) colostrum act as a hormone in the thymus gland by stimulating *thymocytes* (immature lymphocytes) to differentiate and become activated as either helper T-cells or suppressor T-cells.<sup>54</sup> Helper T-cells are a vital part of the immune response which *stimulate* the production and differentiation of cytotoxic T-cells and B-cells, attract white blood cells, and stimulate macrophages to engulf and destroy pathogens. Suppressor T-cells inhibit the production of cytotoxic T-cells to prevent tissue damage and suppress the immune response when no longer needed.
- Promote growth and differentiation of B-cells- PRP promote the growth and differentiation of B-cells, a type of lymphocyte which produces antibodies to antigens, including viral antigens.<sup>55</sup>
- Stimulate Natural Killer cell (NK cell) activity- PRP stimulate the activity of NK cells up to 10 times, far greater than any other known substance. NK cells, along with cytotoxic T-cells, are the cells which actually attack and kill pathogens. NK cells also attack and kill cancerous cells.<sup>56</sup>
- Stimulate the production of tumor necrosis factor-alpha (TNF-a) and interferon-gamma (INF-y)- PRP stimulate production of pro-inflammatory cytokines TNF-a and INF-y, the two major pro-inflammatory cytokines, in white blood cells, peritoneal cells, and placental and amniotic membranes.<sup>57,58,59</sup>
- Promote the proliferation of leukocytes (white blood cells)<sup>60</sup>
- Stimulate production of cytokines by peripheral blood cells-The types of cytokines stimulated by PRP depend on the antigenic stimulation present or the activity state of the immune system (under-productive or over-productive). In one study, mice exposed to herpes simplex virus (HSV) were stimulated to produce large amounts of IL-2 and INF-y and small amounts of IL-10, while mice which had been given transfer factor (PRP) prior to infection responded to HSV by secreting INF-y but no IL-2. PRP stimulates the production of TNF-a, INF-y, IL-6 and IL-10 in blood cell cultures.<sup>61,62</sup>
- Induce differentiation and maturation of monocytes and macrophages<sup>63</sup>
- Increase the permeability of blood vessels in the skin- Part of the inflammatory response to infection is an increase in the permeability of blood vessels in the skin to allow the passage of blood cells and cytokines into the connective tissue to combat the infection. PRP is known to initiate this inflammatory response.<sup>64</sup>

***PRP may assist the immune system in more effectively fighting chronic viral and bacterial infections while simultaneously inhibiting the initiation of inappropriate inflammatory cascades associated with allergy, chemical sensitivity and auto-immune responses.***

• Produce immunity to certain viruses- PRP has been experimentally shown to provide immunity to several viruses, including herpes viruses, Epstein-Barr virus, HIV, measles, vesicular stomatitis virus (a close relative of the rabies virus), and others.<sup>65, 66, 67, 68, 69, 70, 71, 72, 73</sup>

• Inhibit viruses known to be associated with autoimmune diseases- Epstein-Barr virus and human herpes virus-6 (HHV-6) has been associated with chronic fatigue syndrome, an autoimmune disorder. PRP inhibits the replication of both viruses.<sup>74, 75</sup>

• May help down regulate the “cytokine storm” seen in bird flu- Influenza A virus subtype H5N1 sets off a so-called “cytokine storm” which usually results in an often fatal respiratory disease in those infected with the virus. Research has indicated that the storm is caused by cytokine dysregulation which allows pro-inflammatory cytokines to be produced in large numbers, setting off a potentially fatal inflammatory response.<sup>76</sup> As PRP is known to down regulate an overactive immune system, it potentially could be used to put a stop to the overproduction of cytokines and restore homeostasis to the body, preventing a fatal outcome.

• Increase T-cell count in AIDS to normal or near-normal levels- In clinical studies conducted in the nations of Nigeria, Kenya and Zambia in Africa, where AIDS is a particularly devastating disease, PRP oral spray products were shown to boost T-cell (CD4+) levels to normal or near-normal levels in AIDS patients whose T-cell levels prior to treatment were well below normal. Along with the increase in T-cells came a remission of AIDS symptoms within two days of start of treatment, including nausea, vomiting and diarrhea. In the Nigerian study, weight gains of 5% were recorded. Patients taking the PRP spray fared much better in terms of quality of life than did patients on anti-retroviral drugs.<sup>77</sup> Thus the ability of PRP to stimulate the immune response when it is insufficient by inducing the production of new helper T-cells may enable the immune system of AIDS patients to recover sufficiently so that it is able to fight the HIV on its own.

When a mammal is healthy it has an essentially full complement of immune peptides. However, old age, bodily injury, environmental toxins, substance abuse, poor nutrition, excessive stress, suppressed immunity, medication, or illness may result in failure to maintain an optimal array of these types of peptides. In these instances the missing peptide(s), properly processed, prepared and delivered, can be reintroduced into the body. Fortunately, these cells then “instruct” cells to create more copies of the peptides. That is why PRPs are also referred to as “*cytokine precursors*” or “*immuno-modulating peptides*.” Thus, reintroduction of a small amount, even perhaps a single copy of one or more missing peptides, to any infant, teenage, adult or elderly human, or any aged mammal, may quickly return cells in the body to their normal amount of the peptide(s) in question.<sup>78</sup>

Proline Rich Polypeptides are not species specific. PRP from bovine milk works on all mammals, including humans, dogs and cats.<sup>79</sup> As PRP is produced by all mammals and is an entirely natural product, it is generally thought to be safe for all ages. However, lactose is usually associated with PRP and therefore those with milk intolerance may need to proceed with caution. The addition of *lactase*, the milk sugar digesting enzyme, may ameliorate lactose intolerance.

Also, delicate immune system changes occur following conception and during pregnancy. Specifically, there is a shift to Th2 dominance to inhibit the mother’s immune system from over responding to the different DNA of the new life now inside her. Although there are no known reports of colostrum’s interference with full and normal gestation, until further investigation assures safety, caution suggests pregnant women and women hoping to conceive should avoid PRP rich colostrum products unless suggested by their doctor.

#### **Whey Protein Synergists: Glutathione, Selenium and Inulin**

*“Nutrients and other bioactive food components that occur naturally in foods act synergistically with other dietary elements...dietetics professionals have a unique opportunity to promote whole foods.... In addition...functional food products can be developed that further enhance the health benefits of food...a combined functional food and food supplement approach may afford the greatest protection....”*

- J Am Diet Assoc. 1999; 99(10):1278-1285

***...old age, bodily injury, environmental, toxins, substance abuse, poor nutrition, excessive stress, suppressed immunity, medication, or illness may result in failure to maintain an optimal array of these types of peptides. In these instances, the missing peptide(s), properly processed, prepared and delivered, can be reintroduced into the body.***

## Reduced Glutathione

As stated earlier, undenatured whey protein's immunological effect is in no small part likely related to the *glutamylcysteine* groups which act as the substrate for glutathione (GSH) synthesis. These *cystine* groups needed for the intracellular conversion to *cysteine* are in whey and colostral sub-fractions.<sup>80</sup> However, this bioavailable, double bonded cystine portion is very thermo-labile. Denaturation by heat will therefore greatly inhibit the ability of whey proteins to act as precursors to GSH synthesis, though not affecting the biological value of whey as a protein nutrient as such.<sup>81</sup>

*Glutathione* itself is a non-essential nutrient composed of three amino acids: *glutamic acid*, *glycine* and *cysteine*, or more exactly the tripeptide *L-gamma-glutamyl-L-cysteinylglycine*. Availability of cysteine is a limiting factor in the liver's synthesis of glutathione.<sup>82</sup> Monomeric glutathione is also known as *reduced glutathione* and its dimer is also known as *oxidized glutathione* AKA glutathione disulfide. 90% of the glutathione in healthy living cells is in the reduced form.<sup>83</sup>

Glutathione is widely found in all forms of life and plays an essential role in the health of organisms, particularly aerobic ones. In humans, animals, and plants, glutathione is the predominant non-protein *thiol* and functions as an antioxidant, keeping its own -SH groups and related proteins in a reduced condition.<sup>84</sup>

Glutathione is a cofactor for *glutathione S-transferases*, enzymes which are involved in the detoxification of *xenobiotics*, including carcinogens. It is also a cofactor for the *glutathione peroxidases*, which are crucial selenium-containing antioxidant enzymes. It is also involved in the regeneration of ascorbate from its oxidized form, *dehydroascorbate*. There are undoubtedly multiple functions for glutathione yet to be appreciated.<sup>85</sup>

Glutathione is present in the diet in amounts usually less than 100 milligrams daily. It does not appear that much of the oral intake is absorbed from the intestine into the blood, at least in humans. However, there is an occasional study that does show an increase in circulating glutathione after oral administration.<sup>86, 87, 88, 89</sup> There is greater evidence that glutathione may be absorbed into the *enterocytes* where it may help repair damaged cells.<sup>90</sup> Patents have been submitted for reduced glutathione in a *liposome* claiming enhanced absorption.<sup>91</sup>

Chronic functional glutathione deficiency is associated with immune disorders, an increased incidence of malignancies, and in the case of HIV disease, probably accelerated pathogenesis of the disease.<sup>92, 93</sup> Acute manifestations of functional glutathione deficiency can be seen in those who have taken an over-dosage of acetaminophen (Tylenol™). This results in depletion of glutathione in the *hepatocytes*, leading to liver failure and death, if not promptly treated.<sup>94</sup>

Supplemental doses ranges from 50 to 200mg. Oral doses of up to 600 milligrams daily are well tolerated. There are no reports of adverse reactions or over-dosage.<sup>95</sup>

## Organic L-Selenomethionine

Glutathione formation, which we have shown is synergistic with some of whey protein's potential benefits, requires an adequate level of *selenium*. Mammals deficient in selenium have markedly decreased glutathione dependent *peroxidase* activity. Some milk, especially those from New Zealand, tends to be low in selenium. If we assume a dosage level of 12 grams undenatured whey protein as an intake, the recommended levels of selenomethionine just to support the WPI intake is 8 to 12 mcg.<sup>96</sup> However, more optimal levels of selenium are also thought to confer benefits in its own right.

Selenium belongs to the sulfur group of elements which includes oxygen, tellurium and polonium. It is an essential trace element in human and animal nutrition. It is a powerful antioxidant, assists in the regulation of thyroid hormone metabolism and helps regenerate vitamin C from its oxidized state.<sup>97</sup>

Selenium is found in human and animal tissues as *L-selenomethionine* or *L-selenocysteine*. As mentioned, these *selenoproteins* are essential to the endogenous production of the antioxidant proteins, specifically the four glutathione peroxidases (GSHPx 1-4). In addition to its antioxidant activity, selenium may also have immuno-modulatory, anti-carcinogenic and anti-atherogenic activities.<sup>98, 99, 100</sup> It may have activity in detoxification of some metals and other *xenobiotics*, as well as activity in fertility enhancement in males.<sup>101, 102</sup>

Selenium deficiency appears to depress the effectiveness of various components of the immune system. Selenium supplementation in humans has resulted in increased natural killer cell activity.<sup>103</sup> Still, the immuno-modulatory effects of selenium are not well understood.

***Chronic functional glutathione deficiency is associated with immune disorders, an increased incidence of malignancies, and in the case of HIV disease, probably accelerated pathogenesis of the disease.***

The possible anti-carcinogenic activity of selenium is likely related to its antioxidant activity and immune-enhancing activities. In vitro, selenium has been shown to up-regulate *apoptosis* in tumor cells and increase macrophage killing and protect against oxidative DNA damage.<sup>104</sup>

There appears to be an inverse relationship between coronary heart disease and selenium intake. The possible anti-atherogenic activity of selenium may be accounted for, in part, by its antioxidant activity. Glutathione peroxidase may protect low density lipoprotein (LDL) from oxidation, thereby inhibiting atherogenesis and platelet aggregation. (*Lipoperoxides* impair *prostacyclin* synthesis and promote *thromboxane* synthesis).<sup>105</sup>

Selenium has been demonstrated to antagonize the effects of a number of toxic metals, including cadmium and arsenic.<sup>106</sup>

L-selenomethionine is efficiently absorbed from the small intestine via a similar mechanism to that of L-methionine. L-selenomethionine is transported via the portal circulation to the liver where a fraction is extracted by the *hepatocytes* and the remaining amount is transported by the circulation to the various tissues of the body.

Intakes of selenium less than 900 micrograms daily (for adults) are unlikely to cause adverse reactions. Prolonged intakes of selenium of doses of 1,000 micrograms (or one milligram) or greater daily may cause adverse reactions. The most frequently reported adverse reactions of *selenosis* (chronic selenium toxicity) are hair and nail brittleness and loss. Other symptoms include skin rash, garlic-like breath odor, fatigue, irritability and nausea and vomiting.<sup>107</sup>

Selenium is abundant in garlic, onion, broccoli, whole grains and most especially Brazil nuts. The average daily intake of selenium in the United States is reported to be from 60 to 100 micrograms. Optimal daily dosage may be 200 mcg a day.<sup>108</sup>

## Inulins

*Inulins* are naturally occurring *fructose-containing oligosaccharides* (FOS) which are of a class of carbohydrates known as *fructans*. Inulins are of plant origin in which they are naturally synthesized from sucrose. Inulins are present in onions, leeks, garlic, bananas, asparagus, chicory and artichokes. The latter two are the source for most supplemental and functional food sources of inulin. They are sweet tasting and have a smooth texture. As such, inulins are often added to various foods. Inulin intake in the U.S. ranges from 1 to 4 grams daily. It is higher in the European diet.<sup>109</sup>

Inulins, being largely *soluble fiber*, are only slightly digested in the small intestine, their energy content being less than half that of digestible carbohydrates. Non-digestible soluble fibers, typically FOS, that promote the growth of beneficial bacteria in the colon are called *prebiotics*. The FOS is fermented by a limited number of colonic bacteria, especially *bifidobacteria*. Bifidobacteria may inhibit the growth of pathogenic bacteria, such as *Clostridium perfringens* and diarrheogenic strains of *Escherichia coli*. Bifidobacteria and some other bacteria produce the short-chain fatty acids *acetate*, *propionate* and *butyrate*. Energy, in the form of ATP, is produced from the catabolism of butyrate, an important respiratory fuel for the colonocytes.<sup>110, 111</sup>

***In addition to its antioxidant activity, selenium may also have immuno-modulatory, anti-carcinogenic and anto-atherogenic activities. It may have activity in detoxification of some metals and other xenobiotics, as well as activity in fertility enhancement in males.***

Inulins may have antitumor, antimicrobial, hypolipidemic and hypoglycemic actions.<sup>112, 113, 114</sup> They may also help to improve mineral absorption and balance and may therefore have anti-osteoporotic activity.<sup>115, 116</sup> These actions compliment many of the potential benefits of whey proteins and colostrum peptides. Inulin also adds desirable taste and texture benefits to functional food drinks.

Doses up to 10 grams daily are well tolerated. Higher doses may cause such gastrointestinal symptoms as flatulence, bloating and diarrhea.

## Liposomal Delivery

*Liposomes*, “fat bodies” in Greek, have been known within the scientific community for decades. Liposomes are nanosized, self-assembling, membrane-bound mini-capsules composed of phospholipids and related compounds.<sup>117</sup> Phospholipids are unique in that they are bipolar molecules with one end being *hydrophilic* (“water loving”) and the other end being *lipophilic* (“fat-loving”). This means that the liposomes will carry both hydrophilic and lipophilic molecules equally well. The bipolarity of the phospholipid molecules is what accounts for the self-assembly of the membrane when the phospholipids are introduced into a watery environment.<sup>118</sup>

Since the mid-1960’s, liposomes have been recognized as effective carriers of biologically active ingredients to target specific sites of action in a variety of therapeutic applica-

tions. Because liposomes are uniquely versatile, they have been utilized in such applications as cancer therapy, immuno-therapy, and drug delivery.<sup>119, 120, 121, 122, 123</sup> They make absorbable via oral alimentary ingestion otherwise poorly bioavailable small molecules like certain phytonutrients, peptides, and proteins.<sup>124, 125</sup>

Nanosized bioactive peptide chains like PRPs and glutathione are especially subject to degradation by the extremes of PH and enzymes in the digestive tract. This makes their use as functional food ingredients problematic. The use of liposomes is designed to help minimize this problem.

## Conclusion

*“It is the position of the American Dietetic Association that functional foods...have a potentially beneficial effect on health when consumed as part of a varied diet on a regular basis, at effective levels... Knowledge of the role of physiologically active food components, from both phytochemicals and zoochemicals, has changed the role of diet in health. Functional foods have evolved as food and nutrition science has advanced beyond the treatment of deficiency syndromes to reduction of disease risk... Foods can no longer be evaluated only in terms of macronutrient and micronutrient content alone. Analyzing the content of other physiologically active components and evaluating their role in health promotion will be necessary. The availability of health-promoting functional foods in the US diet has the potential to help ensure a healthier population. However, each functional food should be evaluated on the basis of scientific evidence to ensure appropriate integration into a varied diet.”*

- American Dietetic Association Position Paper on Functional Foods Abstract, J Am Diet Assoc. 2004; 104:814-826.

I have attempted in this paper to briefly delineate the rationale and scientific basis for the potential efficacy of a functional food drink mix powder based on the potential benefits of whey protein isolate, colostrum, proline rich polypeptides and the synergistic nutraceuticals glutathione, L-selenomethione and inulin, incorporating a liposomal nanotechnology to promote bioavailability.

***Since the mid-1960's, liposomes have been recognized as effective carriers of biologically active ingredients to target specific sites of action in a variety of therapeutic applications.***

I believe a functional food drink built around these or similar ingredients has great potential for maintaining lean body mass when employing calorie restricted dietary strategies and supporting lean body mass maintenance or recovery in certain disease or injury states. Furthermore, such a functional food also demonstrates potential for supporting endogenous production of antioxidants during free radical stress, and endogenous detoxification related to xenobiotic load, especially in relation to the role of glutathione. Finally such a functional food offers the potential for providing passive immunity benefits while simultaneously modulating active immunity responses.

Certainly many other possible benefits are suggested by this brief review. Future clinical research on functional food formulas focusing on the foods and nutraceuticals covered in this paper is needed to fully demonstrate the actualization of the potential benefits suggested herein.

***Inulins may have antitumor, antimicrobial, hypolipidemic and hypoglycemic actions. They may also help to improve mineral absorption and balance, and may therefore have anti-osteoporotic activity.***

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