BIOACTIVE COMPONENTS OF WHEY AND CARDIOVASCULAR HEALTH

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A growing body of scientific evidence reveals that U.S. whey contains various bioactive components that may have a positive effect on cardiovascular health. Certain bioactive peptides may protect against hypertension through angiotensin converting enzyme (ACE) inhibition and opioid-like activity. Bioactive whey peptides may also be involved in inhibiting platelet aggregation and lowering cholesterol levels. Other whey components such as calcium, magnesium, zinc, B-vitamins, and certain lipid fractions may also help reduce the overall risk of cardiovascular disease.

Food scientists generally favor whey proteins because of their high biological value, excellent functional properties and clean flavor profile. US whey ingredients are used throughout the world in beverages, bars and other food systems. Newer whey ingredients include hydrolyzed whey proteins that contain high levels of bioactive peptides; and milk mineral complex, which is rich in calcium, phosphorus and other minerals.

These two ingredients show particular promise as components of functional foods designed to improve cardiovascular health. Whey ingredients might also be used as components of other foods such as fermented or hyperimmune milk drinks, or products with increased levels of conjugated linoleic acid (CLA), to produce a new generation of dairy products designed to promote cardiovascular health.

WHEY-DERIVED PEPTIDES AND BLOOD PRESSURE

Coronary heart disease is the leading cause of morbidity and mortality in western society. Heart disease is common in every "Westernized" country in the world, and as more countries adopt Western diets and lifestyles, the incidence of heart disease increases steadily worldwide. Important risk factors for heart disease include smoking, hypertension, high blood cholesterol and triglyceride levels, diabetes and genetic disposition. For many years, low fat dairy foods have been recommended as part of a total diet to reduce the risk of cardiovascular disease. Recent research reveals that specific components of whey may also positively impact coronary health.

While the majority of research has involved laboratory and animal studies, further human trails are needed to substantiate the efficacy of whey peptides and other whey ingredients. US whey ingredients are highly valued for their functional and nutritional properties; and the evidence of their cardiovascular benefit is expected to further enhance their popularity as components of regular and functional foods.

BIOACTIVE PEPTIDES

The term bioactivity refers to food components that can affect biological processes or substrates and hence have an impact on body function or condition and ultimately health.

The two major risk factors contributing to the worldwide incidence of cardiovascular disease are hypertension and dyslipidemia. Whey based peptides have demonstrated activity that may reduce both risk factors. Recent research has shown that bioactive whey peptides may be involved in these functions:

- ACE inhibitory activity
- Opioid-like activity
- Antithrombotic activity
- Cholesterol-reducing activity

Whey peptides may also have other functions, including antioxidant activity, which improves overall cardiovascular health.

Whey proteins can be broken down into various bioactive peptides through enzymatic proteolysis. This process can occur during gastrointestinal digestion, by fermentation of milk, or through controlled reactions in the laboratory or whey processing facility. Regardless of the method of hydrolysis, in order to exert antihypertensive activity, the peptides must be absorbed from the intestine in an active form.

Relatively high levels of bioactive peptides could potentially be produced using low amounts of whey. These whey peptides could enter peripheral blood intact and potentially exert systemic effects. The table below shows potential yield of bioactive peptides from ingestion of 1 gram of whey.

Yield of α-lactophorin	35.2 mg
Yield of β-lactophorin	30.2 mg
Yield of serophorin	10.5 mg

Various lactic acid bacteria, including Lactobacillus GG and Lactococcus lactis, have been shown to hydrolyze milk proteins into bioactive peptides. Studies with the antihypertensive peptides from sour milk have shown that these peptides can be absorbed in the digestive system. Research with infants confirms that di- and tripeptides can be easily absorbed in the intestine. Newer studies indicate that fairly long peptides can cross the intestinal barrier in adults and reach the target organ.

When developed as food ingredients, the processing of these peptides is vital to their activity. Severe heat treatment will have a negative affect on the bioavailability of whey peptides, so processors must carefully monitor production parameters. Careful selection of enzymes for proteolysis will result in maximum biological activity and limit development of bitter flavor notes. US whey manufacturers have shown world leadership in manufacturing and testing whey peptides.

ACE INHIBITORY ACTIVITY

Whey peptides have shown angiotensin converting enzyme (ACE) inhibitory activity, both in vitro and in animal experiments. The overall effect of an ACE inhibitor is the control of high blood pressure through dilation of blood vessels and its effect on blood volume.

While angiotensin I is an inactive hormone; angiotensin II is a molecule that directly constricts vascular smooth muscle, thereby increasing blood pressure. It also has numerous other effects on the cardiovascular system, such as decreasing the renal output and increasing water retention. Angiotensin converting enzyme, ACE, converts the inactive angiotensin I into angiotensin II. An ACE inhibitor blocks this reaction by competitive inhibition, and prevents the effects of angiotensin II. ACE also contributes to the inactivation of bradykinin, a potent vasodilator that is also involved in the control of blood pressure.

Several milk-derived peptides have been shown to have ACE inhibitory activity. ACE inhibiting peptides that are derived from casein are called casokinins, while those that are derived from whey are called lactokinins.

ACE is present in a large number of tissues including plasma, kidney, lung and brain. In order to exert an antihypertensive effect in vivo, the Ace-inhibitory peptides must be absorbed from the intestine and delivered to the target organ. While earlier research with sour milk isolated a number of casein fractions with ACE inhibiting and antihypertensive properties, newer studies have shown that numerous whey fractions also possess ACE-inhibiting activity.

Table 1. ACE Inhibitory Activity of Whey Peptides

Peptide	Fragment	Origin	ACE-inhibition (IC50)
YGLF	50-53	α-lactalbumin digestion by pepsin & trypsin	733 µM
YP		Whey of yogurt-like product (L. helveticus)	720 µM
VGINYWLAHKYGL	99-108	α-lactalbumin hydrolyzed by trypsin	327 µM
YGL	50-52	α-lactalbumin hydrolyzed by trypsin	409 µM
WLAHK	104-108	α-lactalbumin hydrolyzed by trypsin	77 µM
VFK	81-83	β-lactoglobulin hydrolyzed by trypsin	1029 µM
LAMA	22-25	b-lactoglobulin hydrolyzed by trypsin	1062 µM
LDAGSAPLR	32-40	β-lactoglobulin hydrolyzed by trypsin	635 µM
CMENSA	106-111	β-lactoglobulin hydrolyzed by pepsin, then trypsin and chymotrypsin	788 µM
ALPMH	142-146	β-lactoglobulin hydrolyzed by pepsin, then trypsin and chymotrypsin	521 µM
VLDTDYK	94-100	β-lactoglobulin hydrolyzed by pepsin, then trypsin and chymotrypsin	946 µM
Captopril		Commercial drug	.006 µM

Adapted from Pihlanto et al., 2000, and Mullally et al., 1997.

In recent research, ACE inhibiting fragments from both α-lactalbumin and β-lactoglobulin were formed by using various enzymes. It has been shown that ACE prefers substrates containing hydrophobic (aromatic or branched side-chains) amino residues at the C-terminal position. Whey fractions hydrolyzed with trypsin alone or a combination of trypsin, pepsin, and chymotrypsin, showed ACE inhibitory activity as outlined in the chart above. ACE inhibition is measured by the concentration of substance needed to inhibit 50% of original ACE activity, (IC50). A lower IC50 value indicates higher efficacy.

Published research studies on ACE inhibitory activity of various whey peptides show results at a level of 77 to 1029 m/M. Several commercially available US hydrolyzed whey protein isolates are currently on the market, which show ACE inhibitory activity in the range of .30 to .50 mg/ml. Captopril, a chemical inhibitor of ACE, is included in the chart for comparison. Peptides derived from food are considered to be milder and safer and to have fewer side effects than the drugs currently used for hypertension treatment. Thus US whey peptides show great promise as ACE inhibitors, and anticipated clinical trials are expected to further substantiate their efficacy.

OPIOID-LIKE ACTIVITY OF DAIRY PEPTIDES

The opioid peptides are those having pharmacological similarities to opium (morphine). The action of the opioid system in cardiovascular regulation is complex, however, endogenous opioid peptides have shown promise as blood pressure modulators. Several whey-derived peptides also exhibit opioid-like activity. These include peptides derived from α-lactalbumin and β-lactoglobulin.

The peptide α-lactophorin has been shown to exert a weak opioid activity to smooth muscles. When injected into the bloodstream, these peptides induce an analgesic and sedative effect on the nervous system. When α-lactophorin was given subcutaneously to conscious, unrestrained spontaneously hypertensive (SHR) and normotensive rats, blood pressure decreased in the SHR rats. This response was blocked by opioid receptor antagonist naloxone, suggesting the opioid receptors were mediating the effect of α-lactophorin.

WHEY INGREDIENTS WITH ANTITHROMBOTIC ACTIVITY AND CHOLESTEROL-LOWERING ACTIVITY

Thrombosis, defined as the formation or presence of a blood clot within a blood vessel, is another major risk factor in cardiovascular disease. Fibrinogen is a plasma protein that is produced in the liver and is converted into fibrin during blood clot formation. The fixation of fibrinogen to the platelets is necessary for platelet aggregation. Milk peptides are believed to inhibit this platelet fixation.

Some whey peptides have been investigated for their antithrombotic activity. Studies demonstrate that a glycomacropeptide (GMP) derived peptide may be involved in platelet binding. Another study also gives limited evidence that lactoferrin-derived peptides may be involved in platelet binding. Further knowledge of roles of whey-derived peptides may show promise in the treatment of thrombosis.

Glycomacropeptide

Glycomacropeptide is formed during the cheese making process. Rennet or chymosin hydrolyses the peptide bond between residues 105 and 106 of k-casein to produce the resulting molecule, GMP, which is eluted in the whey fraction. The C-terminal portion of the molecule contains residues 106-169 from k-casein. GMP comprises 10 to 15% of the protein of whey processed by microfiltration / ultrafiltration. The large GMP molecule can't be absorbed, and must be broken down into smaller peptides to have an effect on blood components.

Casoplatelins are made up of fragments 106-116 of the GMP molecule. These compounds have been shown to inhibit both aggregation and I-fibrinogen binding to ADP-treated platelets. Several other fragments have been shown to have antithrombotic activity: these include fragments 108-110, 106-112, and 113-116. A GMP derived peptide shown to have antihypertensive activity was fragment 108-110.

WHEY PROTEINS AND CHOLESTEROL LEVELS

Whey proteins have also been shown to reduce blood cholesterol levels in animal studies. Elevated LDL-cholesterol and triacylglycerol levels are associated with an increased risk of atherosclerosis. However, there is an inverse relationship between HDL-cholesterol and atherosclerosis. Numerous clinical trials have shown that for each 1% reduction in total plasma cholesterol levels, there is a 2% reduction in coronary events in subsequent years.

In an animal study on albino rats, the use of condensed whey or lactose-hydrolysed condensed whey in yogurt was shown to have a beneficial effect on cholesterol levels. In this study, whole milk and standard yogurt had no hypocholesterolemic effect, but standard yogurt containing lactose-hydrolyzed condensed whey and bifidus yogurts lowered serum cholesterol. In general, yogurts changed HDL-cholesterol little, but tended to raise triacylglycerols. There was marked lowering of LDL-cholesterol in rats given either type of yogurt fortified with whey protein.

A second study found that whey protein lowered liver cholesterol levels when fed at low amounts (10 g/kg feed), and significantly reduced both plasma and liver cholesterol levels when fed at high rates (150 g/kg feed). In another rat study, whey protein versus casein significantly reduced plasma cholesterol concentration by about 35%. The plasma cholesterol lowering, as induced by extra whey protein in the diet, was due to decreases in the VLDL fractions.

Overall, whey peptides exhibit a wide range of bioactive properties, and thus show much promise as components of functional foods. The following table highlights specific bioactive peptides and their function.

Table 2. Other Bioactive Peptides Derived from Whey Protein

Precursor Protein	Fragment	Peptide Sequence	Name	Function
α-lactalbumin	50-53	YGLF	α-lactophorin	Opioid agonist ACE inhibition
β-lactoglobulin	102-105	YLLF	β-lactophorin	Non-opioid stimulatory effect on ileum
β-lactoglobulin	146-149	HIRL	β-lactotensin	Ileum contraction
GMP	106-116 108-110 106-112 113-116	MAIPPKKNQDK	C asoplatelins	Antithrombotic activity
GMP	108-110	IPP		Antihypertensive activity
Bovine Serum Albumin	399-404	YGFQDA	Serophorin	Opioid activity
Bovine Serum Albumin	208-216	ALKAWSVAR	Albutensin A	Ileum contraction ACE inhibition

Adapted from Shah, 2000, and Korhonen et al., 1998.

WHEY MINERALS AND LIPIDS

Milk Calcium/Whey Minerals Complex

Whey is a rich source of calcium, phosphorus, magnesium and zinc. Within recent years, the whey industry has captured these minerals in a new food ingredient know as milk calcium or whey minerals complex. This ingredient serves as a source of calcium supplementation with high purity, and bioavailability. It contains not only calcium, but also other minerals known to be involved in blood pressure regulation. Whey mineral complex shows great potential as an ingredient to fortify dairy and other foods to positively impact cardiovascular health.

Results of NHANES *and* DASH *Studies*

Sodium restriction has been advocated for many years to reduce risk of high blood pressure. However, results of more than 30 epidemiologic studies have assessed the relationship between calcium and blood pressure, and found that inadequate calcium intake is a greater risk factor for hypertension than is excess sodium intake.

The initial evidence of an association between increased dietary calcium intake and lower blood pressure in the United States was reported in 1984, during an analysis of the first National Health and Nutrition examination Survey (NHANES 1.) Since that first evidence was reported, nearly 70 calcium intervention trials in humans have been conducted with various design parameters and study populations.

To better evaluate these diverse studies, meta-analyses have been conducted to determine statistically the effect of increased calcium on blood pressure. One such analysis compared the results of 42 studies and showed significant reduction in blood pressure with higher levels of calcium intake. Results also revealed a greater and more consistent effect in trials that increased calcium intake from food sources which included other minerals, rather than relying on calcium supplementation alone. One advantage of using a whey mineral complex is that it contains a balance of minerals including calcium, phosphorus, magnesium and zinc.

The Dietary Approaches to Stop Hypertension, or "DASH" diet, is another comprehensive study that was designed to assess the effects of dietary patterns and their effect on blood pressure. The DASH diet compared the typical American diet to a diet high in fruits and vegetables that also includes 2-3 servings of low-fat milk or milk products per day. The DASH diet results showed the greatest reductions in blood pressure, with hypertensive participants, who showed an 11.4 mm Hg systolic and 5.5 mm Hg diastolic blood pressure decrease.

A daily intake of 1000 to 1500 mg per day of calcium through a combination of low fat dairy foods and other foods supplemented with dairy calcium is recommended to decrease the risk of hypertension in world populations. Whey mineral complex is becoming the ingredient of choice, especially in the Far East, as a source of these heart healthy minerals.

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is a collective term to describe one or more positional and geometric isomers of the essential fatty acid, linoleic acid. CLA can be found in the milk and meat of ruminant animals and can also be produced synthetically from oils. Dairy products are the principal dietary sources of CLA. Studies have shown that CLA is involved in reducing the risk of heart disease through the following mechanisms:

- Reduces plaque formation
- Causes plaque regression
- Lowers cholesterol
- May act as an antioxidant

Studies on rabbits shows that at a dietary level as low as 0.1%, CLA will inhibit atherogenesis. And at a level of 1%, CLA leads to regression of pre-established plaques.

Also, studies of hamsters fed a diet that included 0.25% or 0.50% CLA showed a significant reduction in fatty streaks or precursors of atherosclerotic lesions.

Sphingolipids

Sphingolipids also show a promising role as protectors against both coronary heart disease and cancer. Whey protein concentrate contains up to 7% lipid material, of which about 50% is phospholipid. Sphingolipids make up 30% of the phospholipids of whey. Long term feeding (two generations) of sphingolipids (1%) to laboratory rats significantly decreased total blood cholesterol levels by about 30%. The potential protective roles of CLA and sphingolipids in cardiovascular health warrant further study.

WHEY AS A COMPONENT OF FUNCTIONAL FOODS

Whey and whey protein concentrate are frequently used to fortify various other dairy products including fermented dairy products. Numerous studies with fermented dairy products and immune milk have shown positive cardiovascular benefit.

The attached formula demonstrates the use of whey protein isolate and hydrolyzed whey protein isolate in a popular type of meal replacement bar.

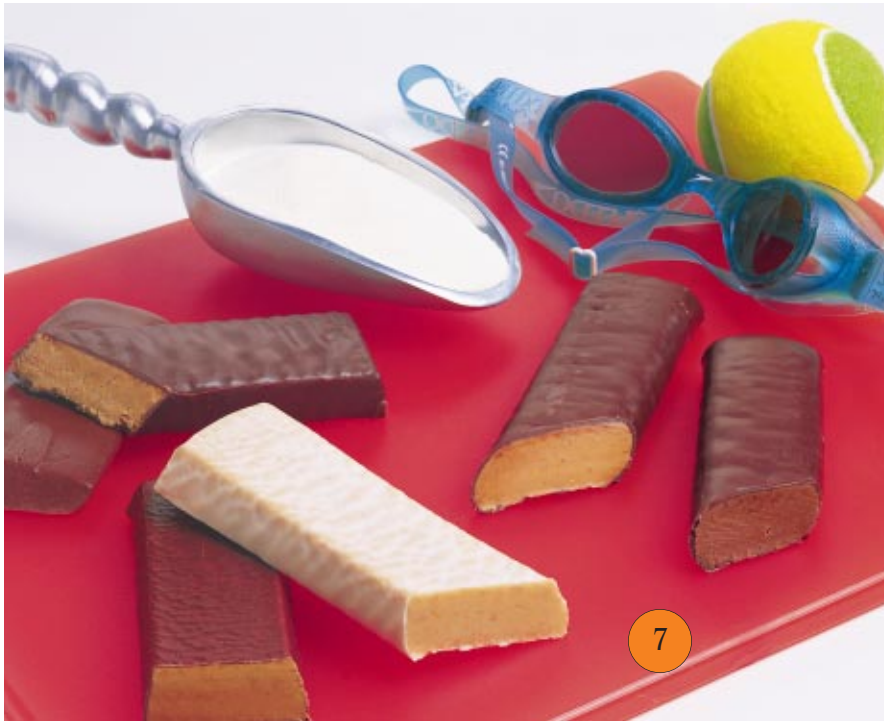
Whey & Peanut Butter Cardiovascular Health Bar* (40% Carbohydrate/30% Protein/ 30% Fat)

Ingredient	%
Honey	18.29
High Fructose Corn Syrup	16.17
Chocolate Coating	14.89
Whey Protein Isolate	**11.12**
Hydrolyzed Whey Protein Isolate	**9.79**
Peanut Butter	8.33
Peanut Flour	7.33
Chopped Peanuts	7.24
Maltodextrin	3.52
Vitamin/Mineral Blend	1.68
Vanilla Extract	1.03
Soy Fiber	0.61
Total	100.00

*Formula courtesy of DAVISCO FOODS INTERNATIONAL, Inc.

Directions for Bench Top Preparation:

1. Place honey, high fructose corn syrup, peanut butter and vanilla extract into KitchenAid mixer with paddle attachment. Blend for 1 minute on medium.
2. Dry blend remaining ingredients, except for chocolate coating. Add to mixer and mix on low speed until all ingredients are evenly incorporated.
3. Extrude or form as desired. Enrobe with chocolate coating.



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