

Proteolytic Enzymes: A Novel Approach in Cardiovascular Dietary Supplementation

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It is estimated that the human heart starts beating around the 3rd week post fertilization and will not stop until the last day of life. Within lifetime, the heart will pump about 6000 liters or 1500 gallons of blood every day. This action of propelling the blood cannot be stopped. It is a vital process to supply all cells with the various nutrients, messenger molecules (neurotransmitters, hormones, cytokines.), enzymes, oxygen but also to remove all metabolite wastes including carbon dioxide from the cellular environment. However, as it performs this indispensable task, it also needs nutrients, protection molecules, various messenger molecules, and oxygen for its function and vitality. Additionally, it requires a timely removal of its various metabolite wastes. The heart is extraordinarily important and must be cared for!

As it pumps this high volume of blood daily and for a lifetime, it needs a complex network of pipelines or blood vessels that deliver the blood to the tissues and remove the wastes. The blood vessels include arteries, veins, and capillaries. It is estimated that there are over 60,000 miles or 100,000 km of blood vessels throughout the body to help carry the blood. Like the heart, this complex network of vessels or pipes and mini-pipes must also be cared for.

The blood is a very dynamic system. Its molecular and cellular composition varies according to the physiological, pathological, developmental, emotional, and nutritional status of the body. Thus, over the years and as a result of many factors, there are conditions such:

- Increased fibrinogen and fibrin clots that impair good blood flow and transport of the various molecules/cells
- Plaque formation within the walls of the vessels (including those supplying the heart) forming possible inflammation sites
- Increased free radicals that damage the heart, vessels, various molecules and cells including erythrocytes (red cells)
- Microorganisms and their metabolites causing injuries to the cardiovascular system
- Increased oxidized proteins (e.g., high oxidized LDL.)
- Glycated proteins (e.g., glycated hemoglobin.) losing their vital functions, and
- Various pollutants (chemicals, medications, inhalants.) causing various injuries to the system.

These various conditions undermine the structure and function of the heart and blood vessels, i.e., the body's pump and pipeline system. Some of the negative consequences include hardening of the arterial walls, narrowing of the blood vessel lumen, weakening of the valves in the veins, and many other patho- physiological conditions.

As the structure and function of the blood vessels are undermined, there is further demand on the heart to maintain a constant supply of blood to all tissues. For instance an artery with a narrowed lumen because of plaques or fatty deposits will require more force from the heart to meet the needs of the body.

Similarly, obesity over-burdens the heart. Although the length of blood vessels per 1 pound of excess body fat varies according to several factors, it is a fact that as fat content increases in the body, so does the length of blood vessels. The estimated blood vessels lengths range from 1 mile per pound of fat to 200 miles per pound of fat. This variation may also be due to the intricate network of capillaries that may or may not be accounted for in the various studies involved in estimating the length of blood vessels around adipose tissues.

This increased length of blood vessels due to fat increases the heart's work load and the blood pressure. Fat cells also need nutrients!

With the increased in body fat, there is also a higher risk of oxidized LDL and plaques along the lining of the blood vessels. This extra load on the heart and the blood vessels will result, for instance, in congestive heart failure, blood clots, and other cardiovascular disorders.

Another major cardiovascular health risk factor that, overtime, may affect most people is the increased sedentary lifestyle which is complicated by the increased sugar consumption in today's society. This set of facts leads to insulin resistance and its health challenge ramifications.

The body's pump and pipeline need continuous support even when symptoms are not noticeable!

It should be mentioned that the absence of noticeable or diagnosed symptoms does not necessarily indicate a clean and healthy cardiovascular terrain.

Studies have also indicated that some medications dealing with cardiovascular conditions have the side effect of "robbing" the heart of a key bioenergetic and antioxidant molecules such as CoQ10, thus impairing its function.

Many other factors affect the structure/function of the heart and thus undermining its vitality. Some of these factors include poor nutrition, high levels of free radicals, poor stress management, imbalanced hormone synthesis/secretion, lack of exercise, and various others.

Thus, in order to address the needs of a continuously working system (i.e., the heart and its vessels) that is subjected to many variables with negative consequences, a product containing nattokinase and other proteolytic enzymes with cardiovascular benefits is recommended.

As mentioned, the role of the pump and the pipeline is to carry the blood throughout the body. The main role of the blood is to supply the cells with nutrients and remove metabolic wastes. This vital function of the blood could be carried out only if the blood maintains a certain level of fluidity and is in proper balance in terms of its pH, cells (red and white cells), hemoglobin, and others molecules and cells depending on the bio-physiological status of the body.

The blood is simply the vehicle with which the body accomplishes its transportation needs. It is a liquid-vehicle. It has to maintain a certain level of fluidity. If it is too thin, it loses its ability to coagulate in a timely manner when needed. This results in various forms of hemorrhages or loss of blood throughout the body.

If the blood is too thick it loses its ability to transport the various nutrients and cells to perform their function in a timely manner and/or to rid the body of waste and toxic materials. This condition of thick blood also favors the onset of many serious diseases including cancer.

ENZYMES USED FOR CARDIOVASCULAR HEALTH SUPPORT

Nattokinase is a fibrinolytic enzyme derived from soybean fermentation. A traditional Japanese food called natto, often eaten at breakfast, is made by fermenting soybeans in presence of a *Bacillus subtilis*.

As a result of this food fermentation process, there are various molecules produced including a proteolytic enzyme with specific hydrolytic action on the blood molecule fibrin. This enzyme was identified, characterized and called nattokinase. The enzyme was further purified from various potential contaminants including vitamin K. Although vitamin K is an important molecule, its presence impedes the beneficial activity of nattokinase.

Since the isolation and purification of the enzyme nattokinase, several other studies have shown that (1) it acts faster than plasmin, (2) its beneficial effect remains in the body longer, (3) and it is absorbed through the intestinal tract into the blood circulation (refs).

Although the enzyme controls hyper-coagulation in the body, it is important that the nattokinase used in dietary supplements be of high purity and free of any molecular contaminants that could inhibit its action or create health challenges such as allergic reactions.

As mentioned above, one of the main target molecules of nattokinase is fibrin. Fibrin is derived from fibrinogen. Its role is to help coagulate blood in the clotting process. Studies have shown that as result of poor diet, lack of exercise, chronic inflammation, excess free radical damage, aging, and other factors, there are high risks of increased clots and poor blood flow. These conditions of poor blood flow can occur without warning at multiple sites along the 100,000 miles of blood vessels. Some of these sites could be at vital locations in the heart, brain or other organs leading to hypoxia, and ischemia, i.e., poor oxygen supply or lack of oxygen respectively.

Lack of blood flow to an organ can lead to further debilitating chronic inflammation or even heart attack or stroke if the clots occur within the heart or the brain respectively. Ensuring proper blood flow is a vital process that should be optimized with active dietary supplement enzymes, nutrients, and other approaches.

In addition to nattokinase, there are other proteolytic enzymes also called proteases often derived from fungi or mushrooms that are also used as dietary supplements for cardiovascular health as well as digestive support. Some of these proteases such as Protease 4.5, Protease 6.0, and/or Protease 3.5 are often used as a blend in formulations to support the circulatory system.

Other enzymes with demonstrated benefits on the cardiovascular system include serratiopeptidase from the silkworm and lumbrokinase from the earthworm. Recently, another enzyme has been isolated from probiotics and was shown to be as effective as the streptokinase in controlling blood flow and removing clots. We are working on further characterization of this enzyme as well as its use in dietary supplement formulations.

In addition to nattokinase and other proteases, some cardiovascular dietary supplement support products contain blend of fungal lipases as well as the coenzyme CoQ10. The lipases help target and hydrolyze the triglycerides. This additional action in such formulations helps reduce the load of triglycerides in the circulating blood, thus preventing any damage to the blood vessels through formation of plaques and other cellular injuries. Additionally, the lipases along with nattokinase and/or other proteases help maintain a good blood flow rheology, ensuring delivery of nutrients, and an overall vitality of the cells.

Other ingredients of relevance in cardiovascular support products include coenzyme Q10 (CoQ10). The presence of CoQ10 also called ubiquinone is very important in cardiovascular health support. This molecule plays a key role in the electron transport chain that is responsible for ATP production. It is also a very important antioxidant. Thus, it contributes in controlling excess free radicals that could damage the cardiovascular system, i.e., pump, pipeline, and blood molecules and cells. It should also be noted that some medications have been shown to "rob" the body or deplete it of its CoQ10. Thus, including CoQ10 in a dietary supplementation is very beneficial.

Hyper-coagulation is a major health risk. It increases the risks of heart attack, stroke, and degeneration of the blood vessels. Additionally, inadequate blood flow has been shown to promote metastasis of tumor cells and chronic inflammation in the body. The use of effective enzymes such as nattokinase, other proteolytic enzymes, and lipolytic enzymes as well as antioxidants is

highly recommended as a comprehensive cardiovascular health management and dietary support.

REFERENCES

Battaglino R A, Huergo M, Pilosof A M R & Bartholomai G B (1991). Culture requirements for the production of protease by *Aspergillus oryzae* in solid state fermentation, *Appl Microbiol Biotechnol*, 35: 292-296.

Cho, I.H., et al., (2004). "Purification and characterization of six fibrinolytic serine- proteases from earthworm *Lumbricus rubellus*". *J of Biochemistry and Molecular Biology*; 37(2) 199-205

Fujita, M. et al., (1993). "Purification and Characterization of a Strong Fibrinolytic Enzyme (Nattokinase) in the Vegetable Cheese Natto, a Popular Soybean Fermented Food in Japan". *Biochemical and Biophysical Research Communications* 197 (3): 1340–1347.

Ghirlanda, G. et al., (1993). "Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study". *Journal of clinical pharmacology* 33 (3): 226–9.

Hall, D.A., et al., (1982). "the effect of enzyme therapy on plasma lipid levels in the elderly". *Artherosclerosis* 43:209.

Kwon, E. Y. et al., (2011). "Production of nattokinase by high cell density fed-batch culture of *Bacillus subtilis*". *Bioprocess and Biosystems Engineering* 34 (7): 789–793.

Mazzone, A., et al. (1990). " Evaluation of *Serratia* peptidase in acute or chronic inflammation of otorhinolaryngology pathology: a multicenter, double-blind randomized trial versus placebo". *J. Int Med Res.* 18:379

Mellors, A., and Tappel, A.L. (1966). "The inhibition of mitochondrial peroxidation by ubiquinone and ubiquinol. *J Biol. Chem.* 241: 4353

Miyaka et al., (1981). "Interaction between *Serratia* protease and human plasma alpha 2-macroglobulin". *J. Biochem.* 89:123

Mortensen, SA; Leth, A; Agner, E; Rohde, M (1997). "Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors". *Molecular aspects of medicine* 18 (Suppl): S137–44.

Sarter, B (2002). "Coenzyme Q10 and cardiovascular disease: a review". *The Journal of cardiovascular nursing* 16 (4): 9–20.

Sumi, H., et al., (1987). "A novel fibrinolytic enzyme (nattokinase) in the vegetable cheese Natto; a typical and popular soybean food in the Japanese diet". *Experientia* 43 (10): 1110

Taussig, S.J., et al., (1988). "Bromelain, the enzyme complex of pineapple (*Ananas comosus*) and its clinical application, an update". *J. ethnopharmacol* 22:191

Thibault, A., et al., (1996). "Phase I study of lovastatin, an inhibitor of the mevalonate pathway, in patients with cancer". *Clinical cancer research* 2 (3): 483–91.

Wang, F., et al., (2003); "Purification, characterization and crystallization of a group of earthworm fibrinolytic enzymes from *Eisenia fetida*," *Biotechnology Letters*, vol. 25:1105– 1109

Zhao, J. et al., (2004); *Earthworm Fibrinolytic Enzymes*, vol. 30 of *Studies in Natural Products Chemistry*, Elsevier, North-Holland, The Netherlands.