Special Report

Nattokinase and Cardiovascular Health

Ralph E. Holsworth, Jr., D.O.

Fibrin is a protein that forms in the blood after trauma or injury. This is essential to stop excess blood loss. There are more than twenty enzymes in the body that assist in clotting the blood, while only one that can break the clot down (plasmin). Bacteria, viruses, fungi and toxins present in the blood also trigger an inflammatory condition resulting in excess cross-linked fibrin. Since there is no danger of blood loss and trauma has not occurred, this cross-linked fibrin will circulate through the blood and will stick to the walls of blood vessels. This contributes to the formation of blood clots, slows blood flow and increases blood viscosity contributing to the elevation of blood pressure. In the heart, blood clots cause blockage of blood flow to heart muscle tissue. If blood flow is blocked, the oxygen supply to that tissue is partially cut off (ischemia) which results in angina and heart attacks, or if prolonged, death of heart muscle (necrosis). Clots in chambers of the heart can mobilize to the brain, blocking blood and oxygen from reaching necessary areas, which can result in senility and/or stroke.[1]

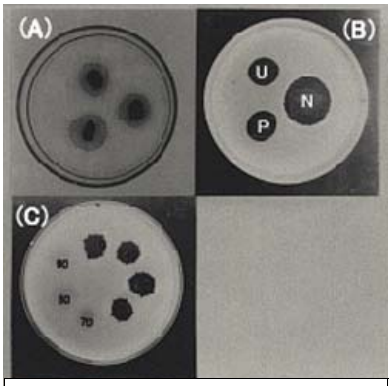

Figure 1

Thrombolytic enzymes (enzymes that break down blood clots) are normally generated in the endothelial cells of the blood vessels. As the body ages, production of these enzymes begins to decline, making blood more prone to coagulation. This mechanism can lead to cardiac or cerebral infarction, as well as other conditions. Since endothelial cells exist throughout the body, such as in the arteries, veins and lymphatic system, poor production of thrombolytic enzymes can lead to the development of blood clots and the conditions caused by them, virtually anywhere in the body.[7]

Figure 2

It has recently been revealed that thrombotic clogging (blood clots) of the cerebral blood vessels may be a cause of dementia. It has been estimated that sixty percent of senile dementia patients in Japan is caused by thrombus. Thrombotic diseases typically include cerebral hemorrhage, cerebral infarction, cardiac infarction and angina pectoris, and also include diseases caused by blood vessels with lowered flexibility, including senile dementia and diabetes. If chronic diseases of the capillaries are also considered, then the number of thrombus related conditions might be much higher. Cardiac infarction patients may have an inherent imbalance. Their thrombolytic enzymes are weaker than their coagulant enzymes. Nattokinase holds great promise to support patients with such inherent weaknesses in a convenient and consistent manner, without side effects. [1,6,7]

Discovery of a Fibrinolytic Enzyme

Dr. Hiroyuki Sumi, M.D. (a.k.a, Dr. Natto) a researcher of the Japan Ministry of Education and majoring in the physiological chemistry at the blood laboratory of the University of Chicago, had long researched thrombolytic enzymes. He was searching for a natural agent that could successfully dissolve thrombus associated with cardiac and cerebral infarction (blood clots associated with heart attacks and stroke). One day in 1980 Dr. Sumi took the natto that he was eating for lunch and dropped a small portion into the artificial thrombus (fibrin) plate (Figure 1). The natto gradually dissolved the thrombus and had completely resolved it in 18 hours! Dr. Sumi found that the sticky part of natto, commonly called "threads" (Figure 2), exhibited a strong fibrinolytic ("blood clot busting") activity. He named the corresponding fibrinolytic enzyme "nattokinase". Dr. Sumi commented that nattokinase showed "a potency matched by no other enzyme." [1,7]

Dr. Sumi conducted research on about 200 kinds of food from all over the world, and he found that natto had the highest fibrinolytic ("blood clot busting") activity among all those foods. There are many traditional foods for the prevention and treatment of thrombosis (e.g., azuki beans, Korean ginseng, Japanese water dropwort) but most of these foods inhibit platelet aggregation

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similar to aspirin. Only nattokinase acts only on the fibrinolytic system to dissolve thrombi within the blood vessels. In 1986, Dr. Sumi presented the results of his research in Japan for the first time at the Japan Agricultural Chemistry Society. Later he wrote a similar article for the International Thrombolytic Association where the audience began to believe that the dietary intake of natto was the major contributor to the longevity of Japanese people.

The Proof is in the Pudding

Nattokinase has been the subject of 17 studies, including two small human trials. Dr. Sumi and his colleagues induced blood clots in male dogs, then orally administered either four capsules of nattokinase (250 mg per capsule) or four placebo capsules to each dog. Angiograms (Figure 3) revealed that the dogs who received nattokinase regained normal blood circulation (free of the clot) within five hours of treatment. Blood clots in the dogs who received only placebo showed no sign of dissolving in the 18 hours following treatment. [1,3]

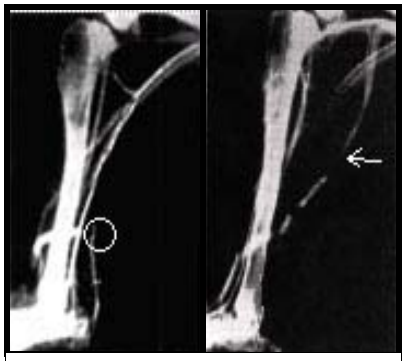


Figure 3

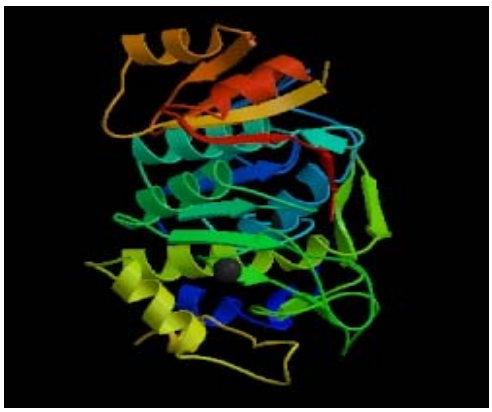
Researchers from Biotechnology Research Laboratories and JCR Pharmaceuticals Co. of Kobe, Japan, tested nattokinase's ability to dissolve a thrombus in the carotid arteries of rats. Animals treated with nattokinase regained 62 percent of blood flow, whereas those treated with plasmin regained just 15.8 percent of blood flow. [1]

Researchers from JCR Pharmaceuticals, Oklahoma State University, and Miyazaki Medical College tested nattokinase on 12 healthy Japanese volunteers (6 men and 6 women, between the ages of 21 and 55). They gave the volunteers 200 grams of natto (the food) before breakfast, then tracked fibrinolytic activity through a series of blood plasma tests. The tests indicated that the natto generated a heightened ability to dissolve blood clots. On average, the volunteers' ELT (a measure of how long it takes to dissolve a blood clot) dropped by 48 percent within two hours of treatment, and volunteers retained an enhanced ability to dissolve blood clots for 2 to 8 hours. As a control, researchers later fed the same amount of boiled soybeans to the same volunteers and tracked their fibrinolytic activity. The tests showed no significant change. [1,3,6]

At Tottori University in Japan, nattokinase therapy is used for treatment of diseases causing thrombosis of the eye grounds with patients who become blind after a blood clot hinders blood flow and weakens the ophthalmic nerve (i.e., vena centralis retinae atresia). Venograms confirm the thrombi, dilation of veins and hemorrhage and subsequent resolution of the eye ground in patients with vena centralis retinae atresia. Patients regained their eyesight within 10 days and no abnormalities observed after 2 months.

Conclusion

Nattokinase is a particularly potent treatment because it enhances the body's natural ability to fight blood clots in several different ways and has many benefits including convenience of oral administration, confirmed efficacy, prolonged effects, cost effectiveness, and can be used preventatively. It is a naturally occurring, food dietary supplement that has demonstrated stability in the gastrointestinal tract. The properties of nattokinase closely resemble those properties of plasmin so it dissolves fibrin directly! More importantly, it also enhances the body's production of both plasmin and other clot-dissolving agents, including urokinase (endogenous). Nattokinase may actually be superior to conventional clot-dissolving drugs such as recombinant tissue plasminogen activators (rt-PA), urokinase, and streptokinase, which are only effective therapeutically when taken intravenously within 12 hours of a stroke or heart attack. Nattokinase, however, may help prevent the conditions leading to blood clots with an oral daily dose of as little as 2,000 fibrin units (FU) or 50 grams of natto.

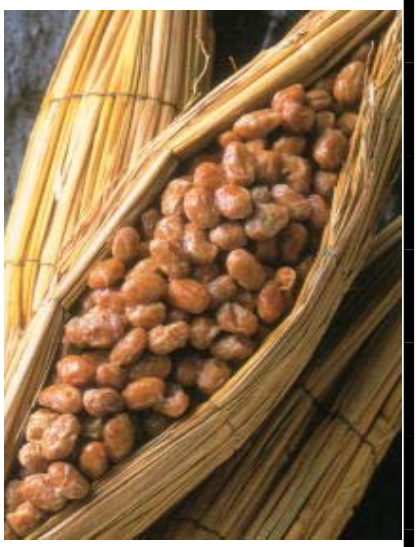


Nattokinase Enzyme

Natto, The Food of Warriors

Ralph E. Holsworth, Jr., D.O.

Say It Ain't Soy! Yes, but this soybean is different! What makes it different is simple. After hours of fermentation, the boiled soybeans metamorphose to an ancient medicinal food called "natto" pronounced "nah'-toe". Natto may just be the "perfect food" producing 18 valuable amino acids and an enzyme nattokinase that may challenge the pharmaceutical industry's best "blood-clot busters". Natto, which has recently attracted attention throughout the world, is the third most popular type of fermented soybean in the Japanese diet. Japan has the highest average longevity in the world, which may partly be attributed to a high consumption of natto.



When compared with ordinary soybeans, the natto produces more calories, protein, fiber, calcium, potassium and vitamin B_2. Its high protein and economical price in terms of protein per gram has earned it the sobriquet "hata-ke no niko," or meat of the field. This nickname appears well deserved, as in comparison with an equivalent amount of beef, natto has slightly less protein (16.5 grams to 21.2 grams), but contains more carbohydrates and fiber, and is also higher in calcium, phosphorous, iron and vitamin B_2. Plus, it has nearly double the calcium and far more vitamin E to boot.

According to legend, the first person to originate traditional Japanese natto was the famous warrior Yoshiie Minamoto during the Heian era of Japanese history (794-1192 A.D.). The horse was an extremely important to the Japanese samurai warrior of the period and great care was given to provide suitable provisions for the horses when armies were on the move. Typically, boiled soybeans were cooled down, dried in the sun and packed immediately in rice straw bags for transport with the army. If the army was on a rapid deployment, the boiled soybeans were packed hastily into the rice straw bags without cooling or drying. The rice straw just happened to contain a harmless and naturally occurring microorganism, Bacillus subtilis that fermented the soybeans and produced natto with its characteristic sticky texture.

Initially, the soybeans were presumed to have spoiled until Yoshiie Minamoto observed that his horses were "picky eaters" and demonstrated a preference for the "spoiled" soybeans or natto. One day, Minamoto demonstrated tremendous courage and dipped his finger into the seemingly "rotten goo". To his astonishment, the fermented soybeans were not only edible but had a distinct Umami flavor. Mimamoto was responsible for introducing natto to northwestern Japan where he ruled. To this day natto is especially popular in that region of Japan and a folk remedy for fatigue, beriberi, dysentery, heart and vascular diseases.

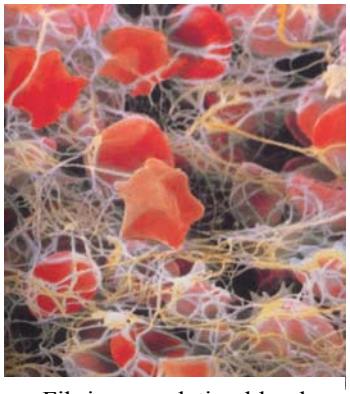
The most distinctive features of natto are the adhesive surrounding the soybeans and the strong flavor. The sticky material has been shown to consist of poly-g-glutamic acid (D and L) and polysaccharides (levan-form fructan) and the strong "cheese-like" flavor is due to the presence of pyrazine. These features sometimes make it hard for some people, especially people from other countries, to accept natto; however, these are the main factors which give natto the outstanding properties. Natto, which has recently attracted attention throughout the world, is a familiar part of the Japanese diet.

Dr. Ralph E. Holsworth, Jr., D.O. is a board-certified Osteopathic Family Medicine Physician. He has been practicing as a family medicine physician with emphasis in functional and integrative medicine for over five years. Dr. Holsworth has had a specific interest in systemic enzyme therapy for ten years and assisted in clinical and laboratory research. He is serving on the medical staff of Mescalero Public Health Service Indian Hospital in Mescalero, New Mexico.

Technical Aspects of Nattokinase

Nattokinase produces a prolonged action in two ways: it prevents the formation of thrombi and it dissolves existing thrombus. Nattokinase orally administrated to twelve healthy adults indicated elevations of the breakdown products of the fibrin and the ability of the blood to breakdown fibrin called euglobulin fibrinolytic activity (EFA). These results suggest the ability of Nattokinase to accelerate fibrinolysis in the blood for a prolonged period of time. FDP levels in the adults drastically increased 4 hours after the administration of the nattokinase indicating that fibrin within the blood vessels is gradually being dissolved with repeated intake of nattokinase. By measuring EFA & FDP levels, the activity of nattokinase has been determined to last from 8 to 12 hours. An additional parameter for confirming the action of nattokinase following oral administration is a rise in blood levels of tissue plasminogen activator (TPA) antigen, which indicates a release of TPA from the endothelial cells and/or the liver and the endogenous production of plasmin (the body's blood clotting buster).[6, 7]

In 1995, researchers from Miyazaki Medical College and Kurashiki University of Science and Arts in Japan studied the effects of nattokinase on blood pressure in both animal and human subjects (see below). In addition, the researchers confirmed the presence of inhibitors of angiotensin converting enzyme (ACE) within the test extract, which consisted of 80% ethanol extract of lyophilized viscous materials of natto. ACE causes blood vessels to narrow and blood pressure to rise - by inhibiting ACE; nattokinase has a lowering effect on blood pressure. [1,2]



Fibrin coagulating blood

The same natto extract was then tested on human volunteers with high blood pressure. Blood pressure levels were measured after 30 grams of lyophilized extract (equivalent to 200 grams of natto food) was administered orally for 4 consecutive days. In 4 out of 5 volunteers, the systolic blood pressure (SBP) decreased on average from 173.8 ± 20.5 mmHg to 154.8 ± 12.6 mmHg. Diastolic blood pressure (DBP) decreased on average from 101.0 ± 11.4 mmHg to 91.2 ± 6.6 mmHg. On average, this data represents a 10.9 percent drop in SBP and a 9.7 percent drop in DBP.[1,2,6]
(See page 8)

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Glossary of Terms

Cardiac Infarction: Heart attack.

Cerebral Infarction: Stroke.

Endogenous: Produced in the body.

Exogenous: Derived from outside the body.

Fibrin: A whitish, filamentous protein formed by the action of thrombin on fibrinogen and makes up part of coagulum or blood clots.

Fibrinolytic: Pertaining to or causing the breaking up of blood clots.

Infarction: Cardiac or cerebral tissue death due to failure of blood supply to the area usually caused by a blood clot.

Plasmin: An endogenously produced fibrinolytic enzyme.

Plasminogen: A precursor to plasmin. A protein found in many tissues and body fluids.

Thrombus: A blood clot that obstructs a blood vessel or a cavity of the heart.

Thrombolytic: Pertaining to or causing the breaking up of a thrombus.

TPA: Tissue plasminogen activator.

t-PAs: The most commonly used thrombolytic drugs including activase, urokinase, and streptokinase.

Urokinase: An endogenously produced thrombolytic enzyme & also a commonly used thrombolytic drug given intravenously to cardiac and cerebral infarction patients.

BLOOD Is Thicker than Water

By Ralph E, Holsworth, Jr., D.O.

Massive research efforts and numerous hypotheses have failed to identify the initiating event of atherosclerosis. Why atherosclerosis develops is significantly more important than how it progresses. To that end, the evolutionary approach to the origin of atherosclerosis is presented and explained based upon the biophysical properties of the blood and their interrelationship with the blood vasculature.

Historically, cardiovascular research has focused on a biochemical approach to atherosclerosis. The results have been a very detailed and accurate histopathology of atherosclerosis, starting with the histological manifestations of fat-laden cells in the intima to the complex series of mechanisms.

However, any theory that embraces only a biochemical, genetic, or environmental perspective leaves many questions unanswered. These question include the following:

- Why are the arteries leading to the heart and brain so susceptible to atherosclerosis?
- Why do we not observe atherosclerotic plaques in the intramyocardial coronary arteries, the arteries of the arms or breasts, or in the veins?
- Why do people with “normal” blood pressure and “normal” cholesterol still have heart attacks?
- Why do men develop cardiovascular diseases at a younger age than do women, especially premenopausal women?
- Why is there a pattern of increased heart attacks in the morning hours (Cannon et al. 1997, Cohen et al, 1997)?

There are simply too many questions that cannot be resolved by applying only current biochemical theories. The fundamental shortcoming of current biochemical theories is that they do not identify the initiating event that precedes endothelial injury (both denuding and nondenuding).

No theory appropriately accounts for the initiating causal factors or factors in atherosclerosis. This is an unsettling fact on an individual and societal level. The cost to the United States in medical care and lost productivity due to cardiovascular diseases is estimated at $298 billion for 2001 (American Heart Association).

An Evolutionary Approach to Atherosclerosis

First, we recognize the human vasculature is a dynamic "organ" that responds to all intrinsic and extrinsic stimuli. Second, we believe that the damaged intima, the lesions, and the occlusions in the vascular system are secondary responses to another event.

The proposed event of mechanical injury as the initiator of the vessel wall injury stems from these shifts in perspective. First, certain types of blood flows may cause mechanical damage to the vasculature. These types of blood flows are referred as *injurious pulsatile flow*. Second, in response to this mechanical injury, the vasculature develops plaques and abnormalities in the vessel wall in a predictable pattern. The presentation of these various mechanisms in a unified concept is called *the protective adaptation theory*. The protective adaptation theory (Kensey and Cho 1992, Kensey and Cho 1994) provides the missing link, particularly in events preceding lesion development, where current biochemical theories cannot account for the mechanisms.

The "Why" of arteriosclerosis and atherosclerosis is eloquently explained by the bellwether work of The Protective Adaptation Theory. Endothelium injury is caused by a high-intensity stimulus over a short period of time, i.e., a coronary artery stent placement. Stress is caused by a low-intensity stimulus over a long period of time, i.e., a callus is a standard adaptation of the skin to stress. A key difference between protective adaptation to stress and to injury is that protective adaptation to stress is usually reversible.

Fluid Mechanics and Hemodynamics

Blood behaves very differently in our circulatory system than water flowing in pipes. First of all, blood has a higher viscosity (thickness) than water. Increased blood viscosity and blood flow is pulsatile and the flow rate varies with time. The reason for the pulsatile flow is two-fold, a resultant of the ejection portion of the cardiac cycle and because the arterial wall is elastic. The arterial system is not a straight pipe with its many bifurcations and bends. Pulsatile blood flow imparts energy into the arterial system that is stored partially in the blood vessels.

The protective adaptation process theory organizes the arterial system's adaptative process into two cycles, both of which originate from the mechanical stresses in the system. The first cycle is the region-specific development of arteriosclerosis, a condition in which the arteries have lost their compliance (elasticity). The second cycle is site-specific development of atherosclerosis in arteries that lost their compliance in cycle one. Although, arteriosclerosis is a precursor to atherosclerosis, the two cycles develop synergistically and reinforce each other in a vicious circle.

Arterial occlusive disease results from a protective response to mechanical stress and injury, a futile effort to maintain the integrity of the vessel.

Region-Specific Protective Adaptation: Arteriosclerosis

At birth, arteries are extremely compliant and stretchable, but over a lifetime these characteristics decrease as a result of the changes in wall tissue structure. The loss of compliance has been defined as medial arteriosclerosis. The changes of compliance in the arterial wall is an adaptative response to the stretching and stress of high arterial pressure, which causes extended, repeated overstretching of the arteries.

Site-Specific Protective Adaptation: Atherosclerosis

Atherosclerosis is an adaptive response that leads to arterial occlusive disease. Starting as a response to the mechanical injury of endothelial cells, atherosclerosis occurs at very specific sites in the arterial system. These frequency of atherosclerosis in these specific sites correlates with their exposure to injurious systolic pressures and repeated stretch-recoil processes. This explains our first question of, "Why the arteries leading from the heart and brain are so susceptible to atherosclerosis?"

Whole Blood Viscosity – The Start of The Pathogenesis

Viscosity represents the stickiness and thickness of blood. It is the frictional resistance to blood flow. So as blood viscosity increases, blood flow decreases assuming that the heart maintains the same systolic pressure. In order for the heart to maintain the same cardiac output, the systolic pressure must increase as the whole blood viscosity increases. Elevated blood viscosity contributes to the arteriosclerosis, atherosclerosis and increased peripheral vasculature resistance. Increased vasculature peripheral resistance results in hypertension and an increased left ventricle requirement to work harder. Eventually the atherosclerosis narrows the lumens in the vascular and the blood pressure gradients increase inversely proportional the 4^{th} power of the lumen's decreased diameter size. Only 25-35 % of the left ventricular ejection flows directly to the peripheral vessels from the arterial system to the veins. As blood viscosity and peripheral vasculature resistance increases, an even large volume remains a "pulsatile mass" hammering the arterioles (greatest pressure gradient) very similar to the "water hammer" in water supply lines.

Get The Fibrinogen Out!

Fibrinogen is a major determinant of both plasma and whole blood viscosity. One of the logical and practical ways to reduce whole blood viscosity is to remove fibrinogen from the blood. Lowering fibrinogen levels limits red cell aggregation and reduces whole blood viscosity and plasma viscosity, especially at lower shear rates (Ehrly 1973).

Natto, made from fermented soybeans, is a traditional Japanese food. Many people enjoy it for its distinctive flavor, enlivened by the activity of ***Bacillus subitilis***. Natto has a long history, and some have theorized that it may even have a prehistoric origin, possibly circa B. C. It has at least been ascertained that natto has been popular since the Edo period, 400 years ago. Originally, natto was utilized as a folk remedy for heart and vascular diseases, fatigue, and beriberi. In 1980, Dr. Hiroyuki Sumi et al. found that natto contains a potent fibrinolytic enzyme, which they named nattokinase.

It was confirmed that oral administration of nattokinase (or natto) produced a mild and frequent enhancement of the fibrinolytic activity in the plasma, as indicated by the fibrinolytic parameters, and the production of tissue plasminogen activator. Nattokinase capsules were also administered orally to dogs with experimentally induced thrombosis, and lysis of the thrombi was observed by angiography (Sumi 1990). It was shown that the oral administration of natto and nattokinase enhance the fibrinolytic activity in plasma. A shortening of euglobulin lysis time (ELT) and an elevation of EFA were found for a long time (from 2 to 8 hr) after a single administration of natto ($p<0.01$) (Sumi 1989).

Conclusion

Nattokinase may prove to be a defibrinogenating enzyme that drastically decreases blood viscosity. Decreasing blood viscosity strikes at the root of arteriosclerosis and atherosclerosis as well as hypertension, peripheral vascular disease and congestive heart failure. The fibrinolytic activity of nattokinase resolves the active process of atherosclerosis and lyses thrombi. The per oral administration, prolonged half-life of 4-6 hours and extremely safe profile show favorably upon nattokinase as the key agent for restoration of vasculature health.

EFFECT OF NATTO DIET ON BLOOD PRESSURE

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In Japan, it is said that taking Japanese traditional fermented soybean, natto, tends to lower the blood pressure. In spite of the knowledge, there has been almost no evidence which proves the efficacy of natto diet on high blood pressure.

In the present study, we first demonstrated that some components of natto had a lowering effect on blood pressure, by administrating natto extract to human subjects and rats.

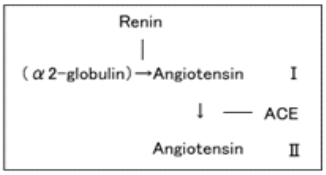


Fig.1 Renin-angiotensin system

We administered a 80% ethanol extract of lyophilize viscous materials of natto. It was reported that the extract contains inhibitors of angiotensin converting enzyme (ACE), which converts angiotensin□to its active form angiotensin (Fig. 1)[1,2].

Fig 2 shows systolic blood pressure (SBP) change after administration of 0.5ml of 80% ethanol extract (equivalent to 25 mg of viscous materials) into the peritoneal cavity of Wister rats (400-500 g, male). Average SBP of 6 rats was 166±14 mmHg before administration. After administration of the extract, SBP decreased significantly to 145±24 mmHg in 2 hours ($p<0.05$), and to 144±27 mmHg in 3 hours ($p<0.05$).

Fig 2

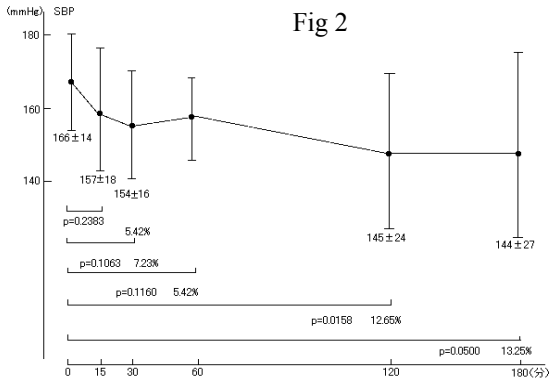
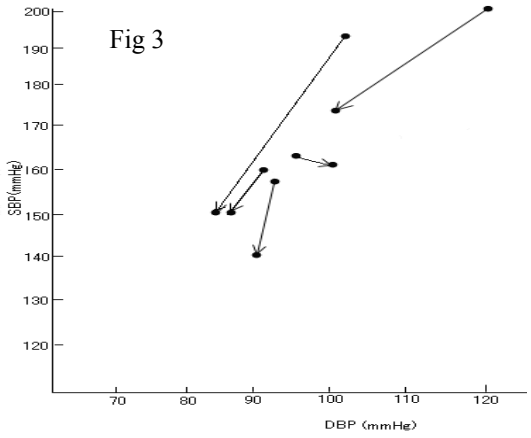


Fig. 3 shows the blood pressure change after oral administration of lyophilized product of 80% ethanol extract to human volunteers who had high blood pressure. Thirty grams of lyophilized extract (equivalent to 200g of natto) was administered per orally for 4 consecutive days. As shown in the figure, in 4 out of 5 volunteers, the SBP as well as diastolicblood pressure (DBP) decreased. The average values decreased from 173.8±20.5 mmHg to 154.8±12.6 in mmHg SBP and 101.0±11.4 mmHg to 91.2±6.6 mmHg in DBP.

For further confirmation of the blood pressure lowering effect of natto, we are going to increase the number of subjects and it is necessary to elucidate the mechanism of the action.

Fig 3



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