
Natto and Its Active Ingredient Nattokinase

A Potent and Safe Thrombolytic Agent

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Natto is a traditional Japanese food made by boiling or steaming soybeans and fermenting them with the *Bacillus subtilis natto*. The bacillus bacteria activate a fermenting process that lends the beans their notoriously sour aroma, nutty flavor, and slippery texture. The *Bacillus subtilis natto* is a rod-shaped bacterium with a relatively high heat tolerance. Compared to other bacteria that have a maximum tolerance of 20°–30°C, *Bacillus subtilis natto*'s heat tolerance is 40°–50°C.

While some researchers have theorized that natto may have prehistoric origins, it first became a part of the Japanese culture during the later part of the Edo Period (1600–1868). During this period, soybeans were packed in straw and buried underground for a week or more. A naturally occurring bacillus in the straw facilitated the soybean fermentation. The result was natto. The modern method of making natto, by injecting the bacillus, was first developed in Sendai.¹

Today, natto is readily available in Japan; it is commonly sold at local grocery stores in portable polystyrene containers. In Japan, natto is prepared several ways, some of which include blended with wheat, miso, cabbage or egg; mixed in salads; as a vegetarian hamburger; or as a condiment. Further research suggests that similar foods exist in other regions of Asia. For instance, people in Nepal make

a comparable fermented soybean product that they refer to as a natto triangle.*

In 1987, Sumi et al. found that natto contained a potent fibrinolytic enzyme that they named nattokinase.² In controlled trials, natto is prepared by adding *Bacillus subtilis natto* to steamed soybeans in polystyrene containers and then allowing the mixture to ferment for 24 hours at 37°C. The natto bacilli are used in a common delivered concentration of 10¹⁰ cells/g of dried bacilli powder.³

Nattokinase

Nattokinase, the active ingredient extracted from natto, is a naturally occurring enzyme with a molecular weight of 20,000 ± 5000. It is heat stable to 60°C with pH solution range of 6–12. Although the human body has several kinds of enzymes for creating thrombi, it uses only one “plasmin” for decomposing and dissolving thrombi. The properties of nattokinase closely resemble that of plasmin. Nattokinase, extracted from natto, is a fibrinolytic enzyme that effectively breaks down fibrin strands and the thrombi this fibrin holds together. Nattokinase has a protein structure made up of a single polypeptide chain consisting of 275 residues of Ala at the N-terminal. It strongly hydrolyzes fibrin. Nattokinase is the most potent fibrinolytic enzyme found among the approximately 200 foods that have been investigated for oral fibrinolytic therapy.⁴ The following discussion clarifies the role of fibrinolytic agents such as nattokinase in the treatment of atherosclerotic and thrombi sequellae, including myocardial infarctions, cerebral vascular accidents, pulmonary emboli, hemorrhoids, ophthalmic thrombi, and other related disorders.

Clot Formation and the Evolution of Atherosclerosis

The evolution of atherosclerosis is a multidimensional process. A patient can simply develop a local thrombus or clot in a coronary artery causing a heart attack; in a branch of the carotid arteries causing a stroke; or in a lower-extremity vein causing a pulmonary embolism if mobilized. As their principal structural component, these clots consist of fibrin strands. Thrombi develop and are maintained via the gradual accumulation of excessive fibrin and/or by the inability of the body to break down the fibrin strands effectively into adequate amounts of fibrin-degradation products.

Clots can form in arteries, in veins, or in the heart chambers. Thrombi in the arteries form under high pressure and flow conditions and are composed of platelet aggregates bound together by intrinsic fibrin strands. Clots in veins form under low flow conditions, are composed predominantly of red cells with few platelets, and contain large amounts of interspersed fibrin strands. These thrombi may remain static in a vessel. However, clots can also become mobile or embolize. If a clot travels from a lower extremity vein to the lungs, the result is a pulmonary embolism. Similarly, if a clot moves from the heart or the carotid artery to the brain, it causes a stroke. And, finally, if a clot travels to a position that occludes or blocks the coronary artery, it causes a heart attack.

There are several other theories involving the formation of occluded vessels leading to heart attacks and strokes. It is generally accepted that, in order for arteries to harden and occlude, platelet adherence must increase. This process is

*Personal correspondences with Kouhei Makise, M.D., Kyoto, Japan.

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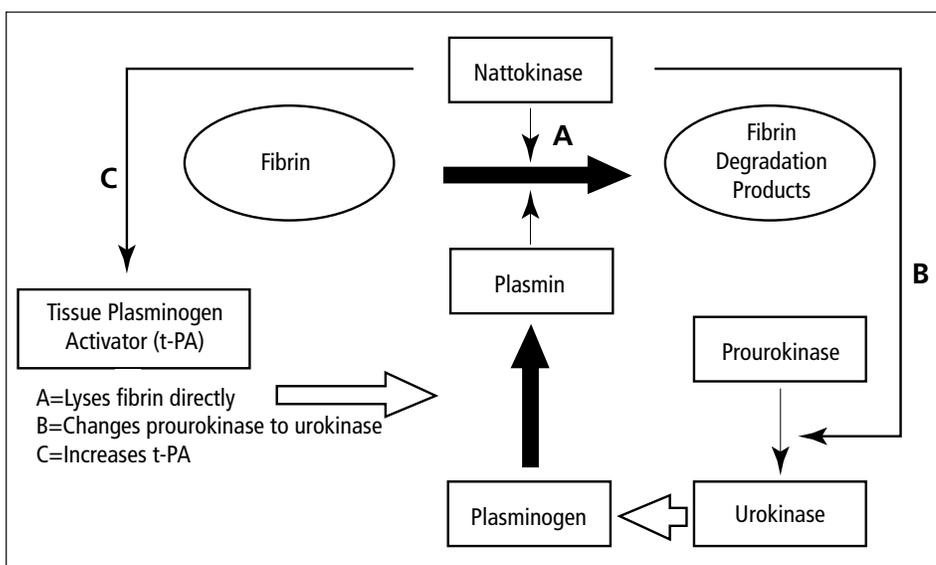


Figure 1. The physiologic effects of nattokinase on fibrin. Nattokinase lyses fibrin directly, (A) changes prourokinase to urokinase (B), and increases tissue plasminogen activator (t-PA).

worsened by excess fibrin. Platelets release a platelet-derived growth factor causing the smooth-muscle cells on the walls of arteries to proliferate. The resultant-smooth muscle cells have an increased permeability to platelets and lipids, especially low-density lipoprotein (LDL). As LDL increases, it penetrates further into the arterial wall. Plaque forms in the arterial wall as a benign neoplastic growth (a monoclonal mutation). Excess fibrin, free radicals, chronic inflammation, oxidized cholesterol, oxidized LDL, environmental hydrocarbons, and other factors aggravate mutation.

According to the free-radical hypothesis, lipid peroxides damage the arterial walls enhancing wall permeability further, as well as additionally increasing the of lipid oxidation, especially that of LDL. Free radicals invade the arterial wall and activate cell proliferation and abnormal cell duplication. The newly mutated cells migrate into the arterial wall and induce plaque formation. This cell proliferation increases the surrounding clot growth or thrombus formation. T-cell antibodies regulate this process. The resulting lesions are atheromatous plaque. The surrounding thrombi form primarily from modified smooth-muscle cells, LDL, and fibrin.

Naturally occurring thrombolytic enzymes that dissolve clots are generated in the endothelial cells of blood vessels. As people age, production of these

enzymes slows and the blood is more prone to coagulate. This causes clotting. However, clots can form at any age. Therefore, it makes good preventive medical sense even for young people to be encouraged to consider the use of a product such as natto or nattokinase for preventive medicine.†

Nattokinase as a Fibrinolytic Agent

It is noteworthy that fibrinolysis (nattokinase's main physiologic effect) is a natural physiologic process. Fibrin, a naturally occurring blood protein is broken up into fibrin-degradation products during fibrinolysis. There are several naturally occurring fibrin-degradation processes, all of which are well-documented in conventional literature. Nattokinase, therefore, undeniably promotes mechanisms of action that occur naturally. Once fibrin is degraded, clotting time is slowed. Nattokinase has been found to lyse (or break down) fibrin strands and plasmin substrates directly.² In the process of clot-regulation, prokinase is converted into urokinase, a process that is enhanced by nattokinase. Breaking fibrin down into its degradation products is also enhanced, converting plasminogen to plasmin. Nattokinase increases tissue plasminogen activator also, enhancing fibrin breakdown and clotting reduction further. By reducing thrombus formation, nattokinase decelerates the progression of plaque formation and reverses evolving atherosclerotic lesions.

The physiologic effects of nattokinase on fibrin are best illustrated in Figure 1. In summary, it is noteworthy that nattokinase lyses fibrin directly, changes prourokinase to urokinase, and increases tissue plasminogen activator (t-PA).

†Personal communication, Hiroyuki Sumi, M.D., Japan Bio Science Laboratory Co., Ltd.

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In an experiment by Sumi et al. (see Figure 2), natto was applied directly to a fibrin plate. Nattokinase was extracted from 300 g of natto with 220 mL of saline for 15 minutes with stirring at 4°C. The material was filtered through gauze and then centrifuged at 3000 rpm for 10 minutes. 10 nL of nattokinase (21 mg of protein/mL), urokinase standard 100 international units/mL, and plasmin standard 4 cu/mL were applied to a fibrin plate.

The nattokinase extract was heat-treated at the temperatures indicated (°C) for 10 minutes and then a 10 μ L sample was applied to a fibrin plate.²

Conventional Thrombolytic Therapy

Conventional thrombolytic therapy entails the intravenous (IV) administration of various thrombolytic agents in hospitalized patients during acute heart attacks. The leading thrombolytic drugs are tissue plasminogen activators (t-PAs), such as Alteplase/Activase[®] and several of its derivatives, including urokinase (Abbokinase[®]), streptokinase, and anecrod. The t-PA is the dominant drug treatment patients who have heart attacks.

All conventional thrombolytic agents work similarly. They convert inactive zymogen plasminogen to the active enzyme plasmin, which then dissolves the fibrin or blood clot. Certain thrombolytics are “fibrin-selective” agents. They work in the absence of systemic plasminogen activation. Yet others are “non-fibrin-selective” agents. They activate systemic and fibrin-bound plasminogen indiscriminately. Nonselective agents cause plasminogen depletion, which results in lower efficacy. There-

fore, fibrin-selective agents (fibrinolytic agents) are considered to be more potent and save an additional 10 lives per 1000 patients.

Conventional thrombolytic or “clot-busting” therapy is given routinely to more than one million patients who sustain acute myocardial infarctions each year. This number represents only a fraction of patients who could actually benefit from the intervention. Conventional interventions have reduced mortality by 30–50 percent, leaving room for alternative therapies.

Another class of therapeutic agents are the platelet antiaggregation products. These agents reduce the platelets’ tendency to clump together by lubricating the platelets and the vessel walls. Dipyridamole, ticlopidine, and clopidogrel are examples of drugs in this category. Bleeding times can be tested to assess optimal platelet aggregation.

There are a number of other over the counter and natural products that inhibit platelet aggregation. Among these are aspirin, fish oil, garlic (*Allium sativum*), coenzyme Q10, bilberry (*Vaccinium myrtillus*), bromelain, ginkgo (*Ginkgo biloba*), Chinese ginseng (*Panax ginseng*), vitamin C, and vitamin E. Of these natural products, Chinese ginseng, bromelain, vitamin E, and, to a lesser extent, garlic produce fibrinolytic activity.

It is important to make a distinction between antiplatelet agents and anticoagulants. Coumarin derivatives such as warfarin (Coumadin,[®] dicumarol, and heparin are examples of anticoagulant agents. These drugs alter the clotting cascade and have a direct effect on clotting times. Overdosing can cause excessive bleeding and hemorrhaging. Prothrom-

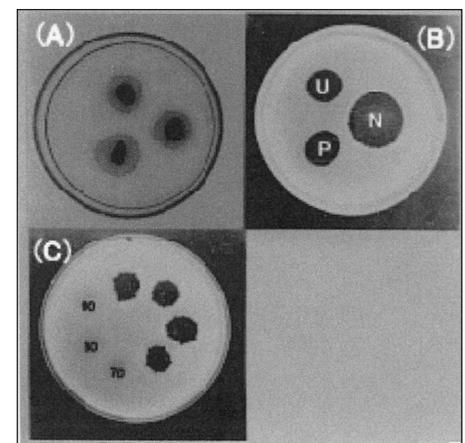


Figure 2. In the experiment above, natto was placed on a fibrin plate (A) and significantly lysed fibrin as shown by the three halos (the larger and clearer the halo, the more fibrin is being degraded). In (B) nattokinase, extracted from natto, was placed on the same fibrin plate next to urokinase (U) and plasmin (P). Nattokinase in vitro more than doubled the amount of fibrin lysis compared to urokinase and plasmin. (C) Nattokinase extract was heat treated at high temperatures of 90°C, 80°C, and 70°C, yet, remarkably, continued to produce fibrinolytic activity. From Ref. 2; reprint permission granted from Daiwa Pharmaceutical Company, Ltd., Tokyo, Japan.

bin time (PT) and partial thromboplastin time (PTT) can be tested to assess optimal clotting time.

Comparison of Fibrinolytic Agents

Nattokinase

Nattokinase has several effects that make it comparable, and in some ways superior, to conventional fibrinolytic drugs. Natto is administered orally. Compared to IV fibrinolytic agents, nattoki-

Natto inhibits fibrin more effectively in-vitro than urokinase or plasmin and is relatively heat resistant.

nase generates fibrin-degradation products for prolonged periods of time. Fibrin-degradation products that result from nattokinase are generated for 8 hours and, in some cases, last up to 12 hours. However, unlike other conventional fibrinolytic agents that are administered orally, natto has been reported to prevent blood coagulation and encourage existing thrombi to dissolve. Intake of as little as 50 g of natto per day has been reported to produce these effects.²

Thrombolytics

Tissue plasminogen activators (Alteplase/Activase). The leading conventional thrombolytic for clots associated with heart attacks is t-PA. This thrombolytic is administered in a hospital setting during an acute myocardial infarction or thrombic stroke. t-PA is most effective within 3–6 hours of onset.⁵ The price of this medication is fairly exorbitant at \$2,200 per dose. However, when dissolvable thrombi are involved, this is the urgent-care intervention of choice. When used in conjunction with heparin, t-PA is considered to be more effective than streptokinase or urokinase. Acute hospital intervention, in many cases, is often too late and ineffective because the vessels of typical patients who sustain heart attacks or strokes contain hardened plaque beyond what a thrombolytic agent can affect.

Urokinase (Abbokinase). In hospital settings, urokinase is often used IV as a fibrinolytic serine protease enzyme to manage atrial heart chamber clots, clots in veins from IV catheters, and during thrombic heart attacks and thrombic strokes. It is indicated for dissolving thrombi in the heart, blood vessels, or lungs. However, as a serine protease, it has been implicat-

ed in tumor growth and metastasis. A large body of research is evolving on the use of urokinase inhibitors to treat early-stage cancers. In comparison to urokinase, which costs approximately \$1,500, 100 g of natto is equally, if not more, effective. Nattokinase maintains its activity for an 8–12 hour period; a longer half-life than urokinase, which is effective for 4–20 minutes.⁶ Nattokinase digests fibrin as well as plasmin substrates.² Natto's powerful fibrinolytic activity was proven in the in-vitro experiment summarized above.² Natto inhibits fibrin more effectively in-vitro than urokinase or plasmin and is relatively heat resistant.

Streptokinase (Streptase®). Streptokinase is often used in urgent-care hospital settings as an IV thrombolytic agent. It is more reasonably priced at approximately \$200 per treatment. It lasts longer than t-PA (approximately 12 hours) and has been reported to cause less bleeding than t-PA.⁷ Streptokinase is indicated for treating an early myocardial infarction, especially an acute anterior myocardial infarction within 6 hours prior to the onset of pain leading to hospital admission. Streptokinase is also indicated for treating acute pulmonary and systemic arterial thrombi. Compared to t-PA, streptokinase has been found to be relatively ineffective when administered soon after a stroke.⁵

Platelet-Aggregation Inhibitors

Aspirin. More than any other medication, aspirin alone is used most often to prevent recurrent strokes and transient ischemic attacks. Aspirin acts by inhibiting blood clotting, which reduces platelet aggregation, and thereby prevents platelet plugs from forming. Aspirin

inhibits cyclo-oxygenase irreversibly, which facilitates thromboxane A2 (TA2) production. TA2 is a potent inducer of platelet aggregation and vasoconstriction. In humans, platelet cyclo-oxygenase can be completely inhibited with aspirin at doses as low as 30 mg per day.

Other conventional platelet-aggregation inhibitors. There are a number of other drugs that act as platelet-aggregation inhibitors, including dipyridamole, ticlopidine, and clopidogrel. The research is contradictory as to whether or not aspirin alone provides better platelet-aggregation inhibition and myocardial infarction–stroke risk reduction than these other drugs do. Studies have also been conducted using aspirin in combination with these other drugs. The results remain inconclusive.⁸

Anticoagulants

Coumarin derivatives. Coumarin derivatives (warfarin and dicumarol) interfere with the rate of synthesis of blood-clotting factors VII, IX, X and II (prothrombin). As a result, PT and PTT are altered significantly by anticoagulants and are not altered by antiplatelet agents. Patients who are taking coumarin derivatives are monitored for PT and PTT to optimize dosing and avoid excessive bleeding.

Heparin. Heparin inhibits thrombosis by inactivating factor X and by inhibiting prothrombin conversion to thrombin. Activation of factor X is the major rate-limiting step in the coagulation cascade.

Natural Products

Bromelain. Bromelain has been well-documented for its ability to activate fibrinolysis via stimulating plasmin production.⁹ Because nattokinase inhibits fibrin more effectively in vitro

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than plasmin, nattokinase is a much more potent fibrinolytic agent than bromelain.

Garlic. Both fried and raw garlic increase serum fibrinolytic activity significantly and reduce fibrinogen and fibrinopeptide by 10 percent.¹⁰ Streptokinase activated plasminogen and fibrinopeptide B β 15–42 are also increased by approximately 10 percent.

Chinese ginseng. *Panax ginseng* has inhibited fibrinogen conversion to fibrin. The herb's mechanism of action appears to be via promoting urokinase's fibrinolytic activity.¹¹

Natto Versus Botanicals and Drugs

Because natto and nattokinase inhibit fibrin invitro more significantly than urokinase does (see the in-vitro experiment discussed above²), logic holds that nattokinase is a more potent fibrinolytic agent than *Panax ginseng* or any other botanical or drug in-vitro. Table 1 and Figure 3 provide a general, comparative guide to the potency of commonly used fibrinolytic agents, based on the extrapolated literature cited above.

Summary of Nattokinase Research

Throughout the 1990s, several researchers reported laboratory findings on various methods of isolating and purifying nattokinase and documented its fibrinolytic activity in-vitro. In 1990, Sumi et al., reported the effectiveness of nattokinase capsules in dissolving experimentally induced thrombi in dogs.¹² There have been at least three studies demonstrating the activity of nattokinase in rats.^{13–15}

One of the more compelling human trials involved 12 healthy Japanese volunteers.¹² Each participant was initially

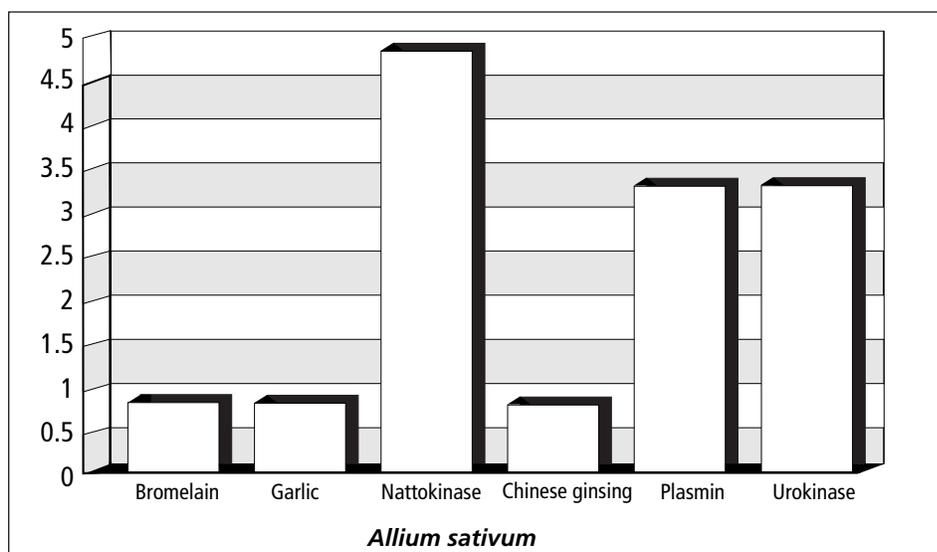


Figure 3. Comparison of commonly used fibrinolytic agents.

Table 1. Potency of Commonly Used Fibrinolytic Agents

Medication	Slight fibrinolysis			Extreme fibrinolysis	
	1+	2+	3+	4+	5+
Bromelain		X			
Garlic ^a		X			
Nattokinase					X
Chinese ginseng ^b					
Plasmin			X		
Urokinase				X	

^aAllium sativum; ^bPanax ginseng.

given 200 g of natto once per day before breakfast, followed by periodic plasma blood testing. After a 2-week interval, the same individuals were given 200 g of boiled soybeans once per day before breakfast. Again, plasma blood was collected. There was just a slight variability in the results of the control groups who

were given boiled soybean. Conversely, the natto-treated group showed a clear shortening of euglobulin lysis time and elevations of euglobulin fibrinolytic activity after a single administration of natto. This enhancement of plasma fibrinolytic activity was maintained for $p < 0.005$ values from 2 to 8 hours after administration.

Enteric coating is essential to protect the enzyme component of nattokinase from gastric acid degradation.

For the same trial, two capsules containing 650 mg of nattokinase were administered three times per day for 8 days. Blood was collected every morning and fibrinolytic parameters were measured in the subjects' serum and plasma. The euglobin fibrinolytic activity in these subjects increased gradually from the first to the eighth day. The subjects' fibrin degradation products were significantly higher on the first day of administration compared to preadministration levels.

In another human trial, Okamoto et al. reported the presence of antihypertensive substances in natto.¹⁶ This was successfully repeated by Murayama and Sumi¹⁷ In this small study, an 80-percent ethanol lyophilized extract of natto was administered to 5 volunteers. In 4 of 5 subjects, average systolic blood pressures fell from 173.8 ± 20.5 mm Hg to 154.8 ± 12.6 mm Hg and diastolic blood pressure fell from 101.0 ± 11.4 mm Hg to 91.2 ± 6.6 mm Hg.

In summary, nattokinase has been the subject of at least 17 studies since 1986. Its fibrinolytic activity has been clearly established in vitro. Five in-vivo efficacy trials were also done and the two human trials were small (5–21 subjects) and were done on a short-term basis.^{12,18}

Indications

Nattokinase as a fibrinolytic agent thins blood and reduces clots and, therefore, encourages neovascularization around occluded arteries. Compounds in natto have been identified as angiotensin-converting enzyme inhibitors, which lower

blood pressure. The following is a list of conditions likely to be ameliorated with use of nattokinase:

- *Atherosclerosis*
- *Coronary artery disease*—via heart attack prevention, morbidity, and recurrence reduction
- *Hypertension*¹⁸
- *Peripheral vascular disease*—arterial atherosclerosis, venous thrombi
- *Strokes*—prevention, and morbidity and recurrence reduction
- *Thrombus formation*—including, venous clots, arterial-wall thrombi with atherosclerosis, atrial-chamber thrombi (as in occurs in chronic atrial fibrillation), hemorrhoids, eye thrombosis (vena centralia retinae acresia), and senile dementia associated with cerebral thrombi formation.

Dosage and Dose Delivery Forms

One study used enterically coated capsules containing 250 mg or 650 mg of nattokinase.¹² The dogs were treated with four 250-mg capsules. In another study, 22 healthy Japanese volunteers (6 men and 16 women) between 21 and 55 were given 200 g of natto before breakfast or 2 enterically coated capsules, containing 650 mg of nattokinase per capsule, 3 times per day after meals.¹² Throughout the literature, dietary doses and experimental doses of natto range from 100–200 grams per day.

Daiwa Pharmaceutical Company, Ltd., Tokyo, Japan, produces one specific brand of nattokinase. It is an enteric coated, highly active, odor-free, and flavorless caplet. Enteric coating is essen-

tial to protect the enzyme component of nattokinase from gastric acid degradation. This is also important because the molecular weight of nattokinase is a size that is generally considered to be too large to be absorbed orally through the gastrointestinal tract. Additional investigation of intestinal absorption research verifies that intestinal absorption takes place for high-molecular-weight compounds up to 33,000 (including urokinase) as a result of intestinal pore size varying from small to large.^{19–24} Daiwa's NKCP natto extract is approximately 0.01 percent nattokinase and contains other proprietary natural substances. The brand's activity is measured using the highest standards and with the plasmin activity test, the only internationally authorized method to measure thrombus lysis. There is no vitamin K in Daiwa's nattokinase. Daiwa recommends a dose of 500 mg daily with each enterically coated caplet delivering 250 mg of NKCP.²⁶

Furthermore, animal studies have shown that nattokinase is completely safe and nontoxic.^{2,25} According to unpublished studies, acute oral toxicity studies show that extremely high doses of nattokinase are not lethal to rats. In addition, a 90-day trial at a wide range of doses demonstrated that nattokinase does not cause gross histopathologic changes.[†]

It is important to make distinctions among the research that has been done with natto, nattokinase, and other manufactured products. In personal correspondences with Dr. Hiroyuki Sumi, he emphasized that Japanese people have

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Dr. Sumi is currently an advisor for Daiwa. His most recent research has been specifically on Daiwa's nattokinase. In our personal correspondence, Dr. Sumi has reported that consumers who eat the equivalent amount of nattokinase in natto and those who take the intrinsic levels of nattokinase in the product experience no side-effects or complications. At the therapeutic dosage recommendation of 500 mg per day, the amount of nattokinase is equivalent to the amount delivered in a 150-g portion of natto. This is the standard dietary amount ingested by many Japanese people for years without side-effects. It is important to reiterate that, while natto contains vitamin K, Daiwa's nattokinase does not. Therefore, additional blood-thinning effects could, in theory, occur as a result of its use, although none has been documented.

Contraindications and Precautions

Thrombic Embolization

Because natto is a very potent fibrinolytic agent it is theoretically possible that regular use could break a clot loose from a lower-extremity vein and cause a pulmonary embolism or pass upward and cause a stroke. In a patient with enlarged atrium chambers or with chronic atrial fibrillation, clots can develop, mobilize, and cause a stroke. However, natto is also naturally high in vitamin K₂. Since the flurry of research began on natto in the 1980s, use of natto as a health-enhancing whole food has dramatically

increased in Japan. In spite of this increase, there have been no reported side-effects, complications or clot mobilizations. Although no controlled studies have been conducted to demonstrate natto's safety with regard to avoiding clot mobilization, historically, documentation records that natto is significantly safe. Because Daiwa's natto extract nattokinase contains approximately 0.01 percent nattokinase and is used at a dose similar to natto, it is conceptually unlikely that therapeutic doses would cause clot mobilization.

Drug Interactions with Coumadin or Other Blood Thinning Medications

The nattokinase in natto could require providers to lower patients' doses of Coumadin. Whether a patient eats natto or takes a nattokinase extract while on Coumadin, it is necessary to take a consistent amount of natto/nattokinase each day. Physicians also need to monitor clotting time (PT, PTT, and international normalizing ratio levels) in the first weeks of natto or nattokinase therapy until these levels are stable.

Conclusion

Nattokinase is an exciting new compound with proven very potent fibrinolytic activity. Natto extracts with significant amounts of nattokinase are promising functional foods. All prior epidemiologic and clinical research points to nattokinase's effectiveness and safety for managing a wide range of diseases, including hypertension, atherosclerosis, coronary artery disease (such as angina),

stroke, and peripheral vascular disease. Evidence from long-term use at high doses in Japanese people points to nattokinase as a safe nutrient that acts as a very powerful fibrinolytic agent. However, more research is needed on humans to verify the predicted safety of formulated extracts that deliver high concentrations of nattokinase while eliminating naturally occurring vitamin K. □

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