MONOGRAPH

Nattokinase
Helps to Support Cardiovascular System Health

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ABOUT AOR
Advanced Orthomolecular Research (AOR) is a Canadian company headquartered in Calgary, Alberta. AOR has an established reputation as the most advanced supplement formulator in the country and around the world. It is through ethical discipline and evidenced-based science that we lead and advance the natural health industry. For more information, please visit aor.ca.

AOR PRODUCT PATH
From raw material selection to manufacturing and shipping of final packaged goods, AOR adheres to the strictest of quality control standards. AOR products represent innovative ideas and thoughtfully researched concepts with advanced techniques to develop products of superior quality and effectiveness, bringing you “innovation you can trust”.

[Diagram of the AOR product path]

Research & Innovation
Formulation & dosage based on leading research

Premium Ingredients
Uphold strict quality policy and supplier qualification programs

Formulation
Use only the minimal required non-medicinal ingredients (NMI) when necessary. Where possible we use NMI declared “clean-label”

Submission to Approval
Receive NPN which means the formula has been assessed and deemed to be safe and effective

Testing of Blended Raw Materials
(Content uniformity and potency)
All bulk finished products (tablets/capsules) are subject to uniformity, disintegration, and potency testing prior to being released to packaging

On-Site Inspection
Sophisticated technologies and validated analytical methods examine incoming raw materials to ensure purity, potency, safety

Blend of Raw Material
In our own state-of-the-art facilities, allowing for complete control over manufacturing

Packaging and Labeling

GMP Quality Control & Third Party Testing
(Microbial, stability and potency)

Finished Product
Approved and cleared for sale/consumption
DIETARY INFORMATION

NPN: 80089368
AOR04121 30 capsules per bottle

Serving Size: 1 capsule

Medicinal Ingredients:
Nattokinase 100 mg* (2000 – 2800 FU†)

* NSK-SD® proprietary nattokinase
† Biofermentation. ‡ Fibrinolytic units.


Suggested Dose: Take one capsule daily, or as directed by a qualified health care practitioner.

Cautions & Contraindications: Do not use this product if you are pregnant or breastfeeding, if you are taking health products that affect blood coagulation or if you have a bleeding disorder. Consult a health care practitioner if you have a cardiovascular, kidney, or liver disorder, or if you are taking any medications. Stop using this product seven days before any scheduled surgery, or immediately if you have unscheduled surgery or if you suffer from an injury resulting in bruising or bleeding. This product is derived from soy. Do not use if you have a soy allergy.

PRODUCT SPOTLIGHT

Nattokinase
Helps to Support Cardiovascular System Health
SUMMARY

WHAT IS NATTOKINASE?

Nattokinase (NK) is a 27,728 kDa, heat resistant (up to 50˚C), serine protease sourced from a Japanese food, called Nattō, which is made from boiled soybeans fermented with a selected strain of Bacillus subtilis var. natto. Other than Nattō, NK would not be be found in other soy foods, due to the fact that nattokinase is only produced through a precise fermentation process, using a specific bacterial strain. Furthermore, this enzyme is only active following ingestion, however, it is not clear whether this activation is direct or indirect.

Interest in the use of nattō and NK arose from research carried out in the 1980s, which investigated food options with thrombolytic properties. This investigation led to the isolation of NK from nattō and more research into the role and benefits of NK in health commenced. NK is used as a health supplement due to its “fibrinolytic” properties (being able to enzymatically degrade fibrin, which is thought to reduce cardiovascular incidents by preventing thrombus formation and subsequent blood clotting). Japan Bio Science Laboratory (JBSL) was the first company to launch Nattokinase as a supplement for human consumption – this was launched in 1998, more than 10 years after its discovery.

BACKGROUND

HEALTH BENEFITS OF NATTOKINASE

Nattokinase is considered generally safe, especially as a supplement form. Research has focused on the heart and cardiovascular benefits of this enzyme. Both animal and human clearly demonstrate that NK provides support to the circulatory system, due to its blood clot dissolving abilities. The effects of NK are considered similar to aspirin (which is a well-known blood thinner) – furthermore, the effects of aspirin on gastric bleeding are usually not associated with NK supplementation.

Currently, there are a number of commercial NK products on the market in Japan, China, EU Countries and the US. The claims on these products range from blood thinning to preventing blood clots and improving blood circulation.

TRADITIONAL USES OF NATTOKINASE

Nattō has been consumed as a traditional food in Japan for thousands of years. The fermented soybean extract is standardized to have NK enzyme activity of 20,000–28,000 fibrin degradation units (FU/g) by assay. Nattō is traditionally consumed in African and Asian culinary practices and commonly used to improve the heart and vascular related illnesses, to relieve fatigue and in the treatment of beri-beri. It has thus been consumed in food without adverse effect for more than 1,000 years (Sumi et al 1987). According to the Japanese Ministry of Agriculture, Forestry and Fisheries, 125,000 tons of soybeans were used for nattō production in 2009 and approximately 150,000 tons of nattō (Three million servings) were consumed in Japan in 2010 (MAFF 2011).
CLINICAL STUDIES

NATTOKINASE IN HYPERTENSION

Blood pressure control is influenced by the renin-angiotensin hormonal complex. Angiotensinogen, a protein produced by the liver, is transformed in the blood to angiotensin I by the enzyme renin. Angiotensin I, in turn, is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II increases blood pressure by constricting blood vessels. Animal studies have demonstrated that nattokinase effectively decreases systolic blood pressure in Wistar Rats, within two hours after intraperitoneal administration. The addition of NK to the diet of hypertensive rats significantly reduced systolic and diastolic blood pressure levels, reductions in plasma fibrinogen levels and plasma angiotensin II levels (Fujita et al., 2011). Clinical research in 86 participants, with pre-hypertension demonstrated a relationship between oral administration of 2000 FU/capsule for eight weeks led to a decrease in renin activity, accompanied by a reduction in systolic (SBP) and diastolic blood pressure (DBP) (Kim et al., 2008). Another study monitored the effect of 2000 FU BID (4000 FU/day) on SBP and DBP. Following administration for four weeks, there was a significant decrease in SBP, compared to the placebo group. These findings suggest that treatment with NK at 2000–4000 FU/day is effective at reducing blood pressure levels in pre-hypertensive and hypertensive individuals.

NATTOKINASE IN MAINTAINING CHOLESTEROL LEVELS

In animal studies, nattō (with the nattokinase content) was shown to prevent atherosclerosis due to reduction in lipid peroxidation and improved lipid metabolism. Further examination demonstrated a decrease in triglyceride and total cholesterol levels in rat models, following three weeks of feeding. A reduction in lipid peroxidation in the liver and aorta were also observed (Iwai 2002).

A randomized, double-blind, placebo-controlled study, where 30 patients with primary hypercholesterolemia were administered 4000 FU (400 mg) NK or placebo twice daily for eight weeks. The NK treated group had a greater reduction in total serum cholesterol levels, when compared to the placebo group. There was also a greater reduction of HDL-C and LDL-C levels after eight weeks, although none of these changes were considered statistically significant. More studies are needed to determine statistically significant benefits of NK in maintaining healthy cholesterol levels (Wu et al., 2009).

ANTI-INFLAMMATORY EFFECTS OF NATTOKINASE

A clinical study suggests that nattokinase has anti-inflammatory activity in subjects with levels of C-reactive protein (CRP) indicative of risk for cardiovascular disease. CRP is an acute phase protein that is recognized as the most characterized biomarker for inflammation. In this acute study, 18 subjects, with three or more documented cardiovascular risk factors, took one dose of 100 mg, equivalent to 2000 FU. Although not statistically significant, due to the number of participants, the results show a reduction in CRP levels, with greater results observed in participants that had the most elevated baseline levels (Jeske et a., 2011 – Unpublished work).
CLINICAL STUDIES (continued)

THROMBOLYTIC AND FIBRINOLYTIC ACTIVITY OF NATTOKINASE

Nattokinase has been shown to degrade fibrin clots both directly and indirectly. Clot lysis assays indicate nattokinase degrades fibrin directly with activity comparable to plasmin. Kinetic assays suggest nattokinase is six times more active than plasmin in degrading cross-linked fibrin (Figure 1 outlines the mechanism of action of NK in fibrin degradation). The fibrinolytic activity of NK has been studied in animal models (dog and rat models). These studies demonstrate the thrombolytic and fibrinolytic activity of NK, with blood flow restoration occurring within hours after administration (Sumi 1990; Fujita 1995). An open label, self-controlled study in healthy volunteers, consuming 2000 FU of NK daily for eight weeks demonstrated fibrinolytic effects. Treatment with NK led to a significant decrease in the plasma levels of fibrinogen, factor VII and factor VIII, to reduce the risk of thrombosis (Hsia et al., 2009). Another study, with single dose administration showed degradation of fibrin/fibrinogen as early as four hours following administration of 2000 FU NK, compared to the placebo group (Kurosawa et al., 2015). In another study, a single oral dose of 30 g lyophilized nattō (200 g original wet weight; estimated to have 6,000 FU) was given to five volunteers (61-86 years old) and blood samples were taken from two to 24 hours after intake. Fibrinolysis was observed for four to eight hours after intake. An important study to consider is the double-blind, placebo controlled study conducted at the Japan Medical School, with 30 adults that were on concurrent medication of warfarin – the hypothesis of this study design was that the addition of nattokinase to the current medication of warfarin would help stabilize the fibrinolytic effects of warfarin, thereby reducing side effects. The results demonstrated that 1700 FU/day of NK for 26 weeks, with concurrent use of warfarin, significantly decreased the rate of change in prothrombin and prothrombin-INR, compared to placebo (Ninomiya 2006).

These studies showed no adverse events during the controlled studies, suggesting that NK is well tolerated, even with the combined administration of warfarin. The potential of NK as an NHP (natural health product) supplement is vast and more research is required to evaluate all the health benefits of NK. Currently, an ongoing clinical study is underway to evaluate the ability of NK in decreasing atherothrombotic risk, as well as slow the progression of atherosclerosis and cognitive decline in a Phase II clinical trial, with 240 participants (ClinicalTrials.gov Identifier: NCT02080520, 2015).
MONOGRAPH NATTOKINASE

PHARMACOLOGY
MECHANISMS OF ACTION

NK can break down blood clots by directly hydrolyzing fibrin and plasmin substrate, converts endogenous pro-urokinase to urokinase (uPA), degrades PAI-1 (plasminogen activator inhibitor-1), and increases tissue plasminogen activator (t-PA) which supports fibrinolytic activity. Unlike common fibrinolytic proteases, such as t-PA and uPA, which can produce various side effects such as bleeding, NK exhibits little to no side effects. Studies also indicate that an oral administration of NK can be absorbed by the intestinal tract. NK exhibits strong fibrinolytic activity after intraduodenal absorption, with an average activity of 40 CU (plasmin units)/gram. NK exhibits fibrinolytic activity at the blood vessel wall, with evidence showing that NK can reduce vessel wall thickening, following endothelial injury. These characteristics make NK a versatile and potent fibrinolytic enzyme that can be used to combat blood clots, without inhibiting the wound healing process overall.

Figure 1: Thrombus dissolving mechanism of Nattokinase.

- Promotes the function of plasmin, a fibrinolysis enzyme by activating pro-urokinase and turning it into urokinase.
- Dissolves directly.
- Degradates and inactivates PAI-1 (Plasminogen Activator Inhibitor -1) increases t-PA (tissue Plasminogen Activator) that promotes degradation, and promotes the function of plasmin.

References:
- a Sumi, H. et al., Experientia, 43, 1987
- b Sumi, H. et al., Yatagai, C., Fibrinolysis, 43, 1996
PHARMACOLOGY (continued)

PHARMACOKINETICS & PHARMACODYNAMICS

More research is needed to completely understand the pharmacokinetic parameters of NK. Current information suggests that orally ingested NK may be absorbed from the intestines. Since NK is similar to Bromelain, in terms of molecular size, it is expected that NK will be able to pass through the intestinal barriers. Rat studies have demonstrated that measured transport of NK occurs across the intestinal tract – following intraduodenal administration, NK was detected in plasma within three to five hours. Furthermore, approximately a half hour following administration in rats, the researchers were able to measure fibrinogen degradation products in the plasma, compared to baseline.

A follow-up pharmacokinetic study was conducted with 11 healthy adults (male and female, ages 21-65 years old) who took a single dose of NSK-SD (100 mg, 2,000 FU). Blood was drawn before and up to 48 hours after ingestion of the NK. The presence of NK in serum was detected via an ELISA assay using a rabbit polyclonal antinattokinase capture antibody. The peak plasma concentration occurred at 13.3 ± 2.5 hours post-dose. NK was significantly increased in serum from 2 to 24 hours post-dose compared to baseline (Ero et al., 2008).

INTERACTIONS & CONTRAINDICATIONS
(E.G., HERB-DRUG, HERB-FOOD, HERB-LABORATORY TESTS ETC.)

There are no documented cases of drug interactions with nattokinase.

CAUTIONS & CONTRAINDICATIONS

Avoid nattokinase in patients with ischemic stroke, peptic ulcer, and coagulation disorders, as well as with concomitant anticoagulant therapy, and pre- and post-surgery. Nattokinase seems to act like a “clot thinner” and might make bleeding disorders worse. Use with caution if taking other anticoagulant/antiplatelet medications.

ADVERSE EVENTS/REACTIONS, SIDE EFFECTS, CAUTIONS OR WARNINGS AND CONTRAINDICATIONS:

Mild adverse effects have been reported in clinical settings. These include diarrhea, common cold, constipation, pimples, stomach pain, menstrual cramps and headaches. There have been no reports of significant weight changes or haematological profiles associated with NK treatment. Supplementation in patients who had suffered a stroke, with 6000 FU/day (for seven days), along with Clopidogrel and heparin, then monitored for three months showed no incidence of hemorrhagic transformation of the infarct. Three adverse events were reported that may be attributed to NK treatment. These include 1) Prolonged activated partial thromboplastin time, 2) moderate hematemesis, and 3) an abnormal liver function test. All of these events were temporary. In a study that looked at the combination of NK and warfarin, no adverse events were demonstrated in the combination or individual treatment group, suggesting that NK is well tolerated in humans.

Case Study: One case study exists in a 52-year-old patient with cerebral microbleeds, in Taiwan (stroke survivor) using daily Aspirin, as well as other antihypertensive agents, who also used 400 mg NK daily for a week. The patient experienced cerebellar hemorrhage attributed to the combination of two anticoagulating agents (Chang et al., 2008). This patient also had high blood pressure and a family history of cerebral hemorrhage. No information was provided after discontinuation of NK.
CLINICAL APPLICATIONS

PHARMACOKINETICS

Nattō has been consumed for thousands of years. Nattokinase supplements have been on the market in China, Japan, Korea, EU Countries and the US. Although no serious adverse side effects have been reported or observed from the consumption of NK in the numerous human clinical trials, the safety profile of NK still needs to be thoroughly assessed. A comprehensive safety data, assembled under GLP compliance protocols, suggests no clastogenic or mutagenic activity in in-vitro models. Although no serious adverse side effects have been reported or observed from the consumption of NK in the numerous human clinical trials, the safety profile of NK still needs to be thoroughly assessed. A comprehensive safety data, assembled under GLP compliance protocols, suggests no clastogenic or mutagenic activity in in-vitro models. Various animal and micro-organism studies have been carried out to assess the safety of NK – these include a single, oral toxicity study, with a maximum dose of 1000 mg/kg/day; a 13-week oral toxicity study using 1000 mg/kg/day; a reverse mutation assay (Ames test); a chromosomal aberration test and pathogenicity study of nattokinase producing bacteria all yielded negative/no influence results.

INDICATIONS AND CLINICAL USE

Nattokinase decreases plasma levels of fibrinogen, factor VII and factor VIII in human subjects

Nutrition research 29 (2009): 190 – 196 Hsia CH. et al.,

Nattokinase, a serine proteinase from Bacillus subtilis, is considered to be one of the most active functional ingredients found in nattō. In this study, we hypothesized that nattokinase could reduce certain factors of blood clotting and lipids that are associated with an increase risk for cardiovascular disease (CVD). Thus, an open-label, self-controlled clinical trial was conducted on subjects of the following groups: healthy volunteers (Healthy Group), patients with cardiovascular risk factors (Cardiovascular Group), and patients undergoing dialysis (Dialysis Group). All subjects ingested two capsules of nattokinase (2000 fibrinolysis units per capsule) daily orally for two months. The laboratory measurements were performed on the screening visit and, subsequently, regularly after the initiation of the study. The intent-to-treat analysis was performed on all 45 enrolled subjects. By use of mixed model analysis, a significant time effect, but not group effect, was observed in the change from baseline of fibrinogen (P = .003), factor VII (P b.001), and factor VIII (P b.001), suggesting that the plasma levels of the three coagulation factors continuously declined during intake; also, the extents of decrease were similar between groups. After two months of administration, fibrinogen, factor VII, and factor VIII decreased 9%, 14%, and 17%, respectively, for the Healthy Group; 7%, 13%, and 19%, respectively, for the Cardiovascular Group; and 10%, 7%, and 19%, respectively, for the Dialysis Group, whereas blood lipids were unaffected by nattokinase. No significant changes of uric acid or notable adverse events were observed in any of the subjects. In summary, this study showed that oral administration of nattokinase could be considered as a CVD nutraceutical by decreasing plasma levels of fibrinogen, factor VII, and factor VIII.
INDICATIONS AND CLINICAL USE (continued)

Effects of nattokinase on blood pressure: a randomized, controlled trial.
Hypertension Research 31, (8) 1583-1588 Kim JY et al., 2008

The objective of this study was to examine the effects of nattokinase supplementation on blood pressure in subjects with pre-hypertension or stage 1 hypertension. In a randomized, double-blind, placebo-controlled trial, 86 participants ranging from 20 to 80 years of age with an initial untreated systolic blood pressure (SBP) of 130 to 159 mmHg received nattokinase (2,000 FU/capsule) or a placebo capsule for eight weeks. 73 subjects completed the protocol. Compared with the control group, the net changes in SBP and diastolic blood pressure (DBP) were -5.55 mmHg (95% confidence interval [CI], -10.5 to -0.57 mmHg; p<0.05) and -2.84 mmHg (CI, -5.33 to -0.33 mmHg; p<0.05), respectively, after the eight-week intervention. The corresponding net change in renin activity was -1.17 ng/mL/h for the nattokinase group compared with the control group (p<0.05). In conclusion, nattokinase supplementation resulted in a reduction in SBP and DBP. These findings suggest that increased intake of nattokinase may play an important role in preventing and treating hypertension.

Consumption of nattokinase is associated with reduced blood pressure and von Willebrand factor, a cardiovascular risk marker: results from a randomized, double-blind, placebo-controlled, multicenter North American clinical trial

Integrated Blood Pressure Control 2016:9 95-104 Jensen GS et al., 2016

Objective: The objective of this study is to evaluate the effects of consumption of nattokinase on hypertension in a North American hypertensive population with associated genetic, dietary, and lifestyle factors. This is in extension of, and contrast to, previous studies on Asian populations.

Materials and methods: A randomized, double-blind, placebo-controlled, parallel-arm clinical study was performed to evaluate nattokinase (NSK-SD), a fermented soy extract natto from which vitamin K2 has been removed. Based on the results from previous studies on Asian populations, 79 subjects were enrolled upon screening for elevated blood pressure (BP; systolic BP ≥130 or diastolic BP ≥90 mmHg) who consumed placebo or 100 mg nattokinase/d for the eight-week study duration. Blood collections were performed at baseline and eight weeks for testing plasma renin activity, von Willebrand factor (vWF), and platelet factor-4. 74 people completed the study with good compliance.

Results: Consumption of nattokinase was associated with a reduction in both systolic and diastolic BP. The reduction in systolic BP was seen for both sexes but was more robust in males consuming nattokinase. The average reduction in diastolic BP in the nattokinase group from 87 mmHg to 84 mmHg was statistically significant when compared to that in the group consuming placebo, where the average diastolic BP remained constant at 87 mmHg (P<0.05), and reached a high level of significance for males consuming nattokinase, where the average diastolic BP dropped from 86 mmHg to 81 mmHg (P<0.006). A decrease in vWF was seen in the female population consuming nattokinase (P<0.1). In the subpopulation with low plasma renin activity levels at baseline (<0.29 ng/mL/h), an increase was seen for 66% of the people after consumption of nattokinase for eight weeks (P<0.1), in contrast to only 8% in the placebo group.

Conclusion: The data suggest that nattokinase consumption in a North American population is associated with beneficial changes to BP in a hypertensive population, indicating that the effects of Nattokinase were more pronounced in the male population.
INDICATIONS AND CLINICAL USE (continued)

A single dose of oral nattokinase potentiates thrombolysis and anticoagulation profiles
*Scientific Reports* 2015;5 11601 Kurosawa Y et al., 2015

Our aim was to determine the quantitative effects of a single dose of Nattokinase (NK) administration on coagulation/fibrinolysis parameters comprehensively in healthy male subjects. A double-blind, placebo-controlled crossover NK intervention study was carried out in 12 healthy young males. Following the baseline blood draw, each subject was randomized to receive either a single dose of 2,000 FU NK (NSK-SD, Japan Bio Science Laboratory Co., Ltd.) or placebo with subsequent crossover of the groups. Subjects donated blood samples at two, four, six and eight hours following administration for analysis of coagulation/fibrinolysis parameters. As a result, D-dimer concentrations at six, and eight hours, and blood fibrin/fibrinogen degradation products at four hours after NK administration elevated significantly (p < 0.05, respectively). Factor VIII activity declined at four and six hours (p < 0.05, respectively), blood antithrombin concentration was higher at two and four hours (p < 0.05, respectively), and the activated partial thromboplastin time prolonged significantly at two and four hours following NK administration (p < 0.05 and p < 0.01, respectively). All the changes, however, were within the normal range. In conclusion, a single dose of NK administration appears to enhance fibrinolysis and anticoagulation through several different pathways simultaneously.

Lipid-Lowering Effect of Nattokinase in Patients with Primary Hypercholesterolemia
*Acta Cardiologica Sinica* 2009; 25:26_30 Wu DJ et al., 2009

**Background:** Nattokinase is a fibrinolytic enzyme isolated from the vegetable cheese nattō. Although research suggests that nattokinase has beneficial effects on lipid metabolism, there is no clinical data on its effects in human patients with hypercholesterolemia.

**Methods:** Thirty patients with primary hypercholesterolemia given instruction on a low-cholesterol diet and treated with 400 mg (4000 FU) nattokinase or placebo twice daily for eight weeks were selected.

**Results:** No significant changes in serum triglycerides, non-HDL cholesterol, total cholesterol/HDL ratio, and LDL/HDL ratio were found in either treatment group. There was a tendency of greater reduction of total serum cholesterol in the nattokinase group than in the placebo group (-6.15 and -6.8 after four and eight weeks treatment, respectively). There were also greater reductions of HDL-C and LDL-C after eight weeks in the nattokinase group (-10.85%, -6.3% respectively) but no statistically significant was noted.

**Conclusion:** In adults with primary hypercholesterolemia, nattokinase is well tolerated and in combination with a low-cholesterol diet, it may have effects on the serum cholesterol profile.
SAFETY SUMMARY

Nattō has been consumed for thousands of years. Nattokinase supplements have been on the market in China, Japan, Korea, EU Countries and the US. Although no serious adverse side effects have been reported or observed from the consumption of NK in the numerous human clinical trials, the safety profile of NK still needs to be thoroughly assessed. A comprehensive safety data, assembled under GLP compliance protocols, suggests no clastogenic or mutagenic activity in in vitro models. Although no serious adverse side effects have been reported or observed from the consumption of NK in the numerous human clinical trials, the safety profile of NK still needs to be thoroughly assessed. A comprehensive safety data, assembled under GLP compliance protocols, suggests no clastogenic or mutagenic activity in in vitro models. Various animal and micro-organism studies have been carried out to assess the safety of NK – these include a single, oral toxicity study, with a maximum dose of 1000 mg/kg/day; a 13-week oral toxicity study using 1000 mg/kg/day; a reverse mutation assay (Ames test); a chromosomal aberration test and pathogenicity study of nattokinase producing bacteria all yielded negative/no-influence results.

In human clinical studies, no adverse effect level (NOAEL) was found when healthy human volunteers orally consumed up to 10 mg/kg NK for 28 days. There were no significant changes in urine, blood pressure or pulse. The current recommended dosage for NK is 100 mg/day (European Food Safety Authority). Other recommendations suggest 100 mg, twice daily. At this dosage, there are very low toxicological concerns. Clinical safety evidence with doses ranging from 10 mg/kg to 400 mg/day has reported no toxicity related to treatment in a controlled setting (EFSA 2016).

Long-term safety of nattokinase supplementation is supported by its presence in the Japanese food, nattō: Nattokinase is the predominant enzyme found in the popular Japanese fermented food, Nattō. Nattō has been consumed in Japan for at least 1500 years, which establishes a long history of safe, daily consumption of nattokinase. Shurtieff & Aoyagi (2007) estimate that 169,000 metric tons (169 million kg) of nattō was consumed in Japan in 1982, with a per capita consumption of 1.42 kg nattō per year. More recent figures released by the Japanese Ministry of Agriculture, Forestry and Fisheries (2010) report that 125 000 tons (125 million kilograms) of soybeans were used for nattō production in 2010. According to Japanese Bio Science Laboratory (JBSL), the average serving of nattō is about 50 g, which has a fibrinolytic activity of 1500 FU (JBSL, 2008). It is worthwhile, therefore, to note that the amount of nattokinase consumed regularly as nattō by the Japanese population is comparable to the recommended dosage of purified nattokinase as a dietary supplement (50–100 mg nattokinase; 1000–2000 FU per day). In addition to its widespread consumption as a food, the safety of nattō has also been clinically tested.

In addition to the discussion of nattokinase as a known component of the commonly consumed food, nattō, clinical evidence with nattokinase is becoming abundant. First, Wu et al (2009) report an eight-week study in which 30 hypercholesterolemic patients were treated with 800 mg/day (8000 FU/day) nattokinase. The authors mention that there were not any adverse events or significant differences in routine hematological and biochemical tests between treatment and placebo groups.
REFERENCES


13. Protein Data Bank: https://www.ebi.ac.uk/pdbe/entry/pdb/4dww


