

# Nattokinase



**Note:** Nattokinase fibrinolytic activity units (FU) refer to the enzyme activity levels. Enzyme potencies are typically measured according to their activity levels, as opposed to amounts in milligrams that provide no information on activity.

## INGREDIENTS

**Nattokinase** is a naturally-occurring proteolytic enzyme with research on its health benefits spanning decades. Proteolytic enzymes, as the term implies, break down proteins. Nattokinase was discovered in the 1980s when Dr. Hiroyuki Sumi studied 173 kinds of natural foods in an attempt to find a suitable protease enzyme to support circulatory health.

Nattokinase is a serine protease and is derived from natto, a traditional Japanese, fermented, soybean food meal that has been consumed for over a thousand years. Multiple authors have described the significant effects of natto. Nattokinase has been growing in popularity as a dietary supplement for cardiovascular health.\*

## BENEFITS

Helps:

- Support cardiovascular health\*
- Support healthy blood pressure already in normal range\*
- Promote healthy circulation\*

## EXTENDED BENEFITS

### Nattokinase Supplements Make Their Way into The Bloodstream\*

A human clinical trial intended to (1) detect nattokinase directly and immunologically, (2) show that nattokinase and/or its metabolites were detectable in human blood following ingestion of a commercial preparation, and (3) chart a pharmacokinetic dosing effect for nattokinase. Eleven healthy human subjects (five male, six female, ages 21-65) orally ingested a 2000 FU nattokinase capsule immediately following a baseline blood draw. Subsequent blood draws occurred over 24 hours. The presence of nattokinase in serum was measured by an enzyme-linked immunosorbent assay (ELISA), using a rabbit, polyclonal, anti-nattokinase-capture antibody. A pharmacokinetic pattern was observed for nattokinase between baseline and 48 hours post dose. The researchers concluded that their results

provide evidence that nattokinase can be measured directly in the blood of humans after oral ingestion.<sup>1</sup>

### Supports Healthy Blood Pressure\* Supports Healthy Circulation\*

The nattokinase in this formulation is proven from human and corroborative animal studies to support various aspects of the cardiovascular system. In a randomized, double blind, placebo-controlled trial, 86 men and women (ages 20-80) received one capsule per day for 8 weeks containing either nattokinase (at a dose of 2,000 fibrinolytic activity units) or placebo.<sup>2</sup> This trial provided evidence that compared to placebo, nattokinase can significantly help to maintain a healthy blood pressure.

Similarly, another study investigated effects of nattokinase on in vitro platelet aggregation and in vivo thrombosis. Rabbit platelet-rich plasma was incubated with nattokinase and aggregation inducers collagen and thrombin, then platelet aggregation rate was analyzed. Nattokinase significantly inhibited both the collagen- and thrombin-induced platelet aggregations. Nattokinase also reduced thromboxane B2 formation from collagen-activated platelets in a concentration-dependent manner. The results indicate that nattokinase extracted from fermented soybean inhibit platelet aggregation by blocking thromboxane formation, and thereby delay thrombosis. The researchers concluded that nattokinase could be a good candidate, without adverse effects, for improvement blood flow improvement.<sup>3</sup>

Another study assessed the effects of nattokinase on red blood cell (RBC) aggregation and blood viscosity. Blood samples were incubated with nattokinase for 30 minutes at 37 degrees C. RBC aggregation was measured using a Myrenne MA-1 aggregometer and blood viscosity assessed over 1-1000 s(-1) with a computer-

## Supplement Facts

Serving Size 1 veggie capsule  
Servings per container 90 & 270 servings

	Amount per serving	% Daily Value
Nattokinase (enzyme activity in fibrinolytic units)	2,000 FU	†

† Daily Value not established.

**Other Ingredients:** Modified cellulose (vegetarian capsule), maltodextrin, magnesium stearate (vegetable source).

### Contains Soy

**Suggested Adult Use:** Take 1 capsule daily, between meals, or as recommended by a nutritionally-informed physician.

**Warning:** Do not use this product if you are pregnant or nursing, are allergic to soy, or if you are taking blood-thinning medication, consult a physician before taking this product.

**Non-GMO / Gluten Free / Vegan**

Store in a cool dry place.

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controlled scanning capillary rheometer (Rheolog). In vitro results showed a significant, dose-dependent decrease of RBC aggregation and low-shear viscosity, with these beneficial effects evident at concentrations similar to those achieved in previous in vivo animal trials. The study concluded that the data indicates positive in vitro hemorheological effects of nattokinase and suggest its potential value as a therapeutic agent.<sup>4</sup>

Research in rats not only confirmed this effect and its potential mechanisms, but also demonstrated that nattokinase retained its protease activity after intestinal absorption.<sup>5</sup>

Other types of research advance the notion that nattokinase can help maintain circulatory and vascular health.<sup>6-8</sup> In a human clinical trial, both natto and nattokinase were administered (soybeans were used as a control), and various features of protease activity were measured in the bloodstream<sup>9</sup>

Another study attempted 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, cross-over 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 or placebo with subsequent cross-over of the groups. Subjects donated blood samples at 2, 4, 6- and 8-hours following administration for analysis of coagulation/fibrinolysis parameters. The study concluded that a single-dose of NK administration enhances fibrinolysis and anti-coagulation via several different pathways simultaneously.<sup>10</sup>

Another study examined whether nattokinase could reduce certain factors of blood clotting and lipids. An open-label, self-controlled clinical trial was conducted on subjects that included healthy volunteers. The healthy subjects ingested 2 capsules of nattokinase (2000 fibrinolysis units per capsule) daily orally for 2 months. Laboratory measurements were performed on the screening visit and regularly after initiation of the study. After 2 months, fibrinogen, factor VII, and factor VIII decreased 9%, 14%, and 17% for the Healthy 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. The study concluded that oral administration of nattokinase could be considered as a nutraceutical by decreasing plasma levels of fibrinogen, factor VII, and factor VIII.<sup>11</sup>

A related study showed that nattokinase (NK) can promote healthy brain circulation and function through multiple mechanisms. Researchers examined the level of cyclic Adenosine Monophosphate (cAMP) and the pathway of the Janus Kinase1/Signal Transducers and Activators of Transcription1 (JAK1/STAT1) in vivo. Also, Ca(2+) mobilization in human platelet stimulated by thrombin was observed in vitro. In addition, vasomotion of vascular smooth muscle was measured by adding KCl or norepinephrine(NE) under Ca(2+) contained bath solutions. The effect induced by NE in the presence of N-nitro-L-arginine methyl ester (L-NAME) or indomethacin (Indo) was also detected. Finally, levels of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1) in cultured supernatants in Human umbilical vein endothelial cells (HUVECs) were measured by ELISA kit. The researchers concluded that their data indicate the neuroprotective effect of NK was associated with its antiplatelet activity by elevating cAMP level and attenuating calcium release from calcium stores; with its anti-apoptotic effect through the activation of JAK1/STAT1 pathway; and its relaxing vascular smooth muscle effect by promoting synthesis and release of NO, reducing Ca<sup>2+</sup> influx, plus its protection of endothelial cells through increasing fibrinolytic activity and facilitating spontaneous thrombolysis.<sup>12</sup>

### Nattokinase Safety\*

Recent studies have reported nattokinase administration in humans, with no indication of adverse effects. To evaluate the safety of nattokinase in a more comprehensive manner, several GLP-compliant studies in rodents and human volunteers have been conducted with nattokinase. Nattokinase was non-mutagenic and non-clastogenic in vitro, and no adverse effects were observed in 28-day and 90-day subchronic toxicity

studies conducted in Sprague-Dawley rats at doses up to 167 mg/kg-day and 1000 mg/kg-day, respectively. Mice inoculated with  $7.55 \times 10^8$  CFU of the enzyme-producing bacterial strain showed no signs of toxicity or residual tissue concentrations of viable bacteria. Additionally, consumption of 10 mg/kg-day nattokinase for 4 weeks was well tolerated in healthy human volunteers.

These findings suggest that the oral consumption of nattokinase is of low toxicological concern. The 90-day oral subchronic NOAEL for nattokinase in male and female Sprague-Dawley rats is 1000 mg/kg-day, the highest dose tested.<sup>13</sup>



## SCIENTIFIC REFERENCES

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