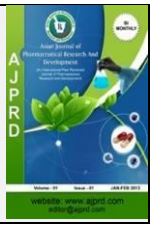
Available online on 15.08.2026 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research



Open Access

Review Article

Biotex Natto+: A Polyherbal Nutraceutical Targeted For Cardiovascular Health.

Polineni Sahithi[3*], Rebello Leroy[1], Chepyala Sreesudha[2]

Research & Development Division, Biotex Life Solutions Pvt Ltd, Secunderabad, Telangana, India.

ABSTRACT

Objective(s): To assess clinical, preclinical, regulatory and safety evidence on the efficacy of nattokinase in cardiovascular health and the rationale for the combination formulation of Biotex Natto+ (nattokinase 250 mg, bromelain 250 mg, standardised nanocurcumin 50 mg).

Data Sources: Relevant published studies were retrieved from PubMed, Scopus and Google Scholar.

Study Selection: Published clinical trials, systematic reviews, meta-analyses and preclinical studies with methodological rigour investigating the effect of nattokinase and/or combination therapy on blood pressure, fibrinolytic activity, haemostatic factors, atherosclerosis and carotid intima-media thickness were selected.

Summary of Contents: Cardiovascular diseases are the leading cause of death worldwide despite the availability of effective pharmacological interventions. Nattokinase is a 27.7 kDa subtilisin-like serine protease from natto that has been extensively investigated as a fibrinolytic nutraceutical. Clinical studies provide preliminary evidence on the antihypertensive, fibrinolytic, anti-inflammatory and anti-atherosclerotic effects of nattokinase. Moderate decreases in systolic and diastolic blood pressures and plasma fibrinogen, coagulation factors VII and VIII were reported alongside improvement in carotid intima-media thickness. Bromelain and curcumin nanoparticles may contribute additional cardioprotective effects, although evidence on the formulated product is indirect.

Conclusion: Nattokinase possesses cardioprotective properties and further clinical studies are warranted to establish the efficacy of the formulated product, Biotex Natto+.

Keywords: Biotex Natto, Polyherbal Nutraceutical, Cardiovascular Health

ARTICLE INFO: Received 19 Jan. 2025; Review Complete 27 March, 2026; Accepted 23 June. 2026; Available online 15 August 2026

Cite this article as:

Sahithi P, Leroy R, Sreesudha C, Biotex Natto+: A Polyherbal Nutraceutical Targeted For Cardiovascular Health., Asian Journal of Pharmaceutical Research and Development. 2026; 14(4): 101-109 DOI: http://dx.doi.org/10.22270/ajprd.v14i4.1855

*Address for Correspondence:
Polineni Sahithi, Research & Development Division, Biotex Life Solutions Pvt. Ltd., Secunderabad, Telangana, India

INTRODUCTION:

Global mortality of 18.6 million deaths is caused by cardiovascular disease. This disease pathology integrates endothelial dysfunction, platelet activation, impaired fibrinolysis, inflammation, and dyslipidaemia[7]. Despite the prominent pharmacotherapy, residual risk, incomplete adherence, and bleeding liability persist8, motivating multi-target nutraceuticals[9]. Since Sumi isolated Nattokinase, the fibrinolytic enzyme from the fermented soybean food natto, substantial cardiovascular evidence has accumulated [2]. This review critically appraises nattokinase pharmacology and evaluates Biotex Natto+, which pairs it up with bromelain and nanocurcumin[10].

Product profile of Biotex Natto+

Biotex Natto+ (Figure 1) is marketed as a vegetarian nutraceutical capsule for adults as an add-on to cardiovascular wellness support, a broader lifestyle programme[10]. As stated by the publicly accessible product specifications, each serving delivers nattokinase enzyme 250 mg, pineapple (*Ananas comosus*) fruit extract 250 mg, and standardised nanocurcumin® from *Curcuma longa* rhizome 50 mg, encapsulated in HPMC shells[10]. The product is manufactured in a GMP-certified facility in Hyderabad, India, and has approval under the FSSAI nutraceutical regulatory framework[10,11].

From a formulary perspective, Biotex Natto+ occupies the multi-ingredient combination tier of the global nattokinase market, which is different from single-ingredient products such as the NOW Foods, Doctor's Best, and Healthy Origins capsules and from clinical-grade NSK-SD®-based preparations as in Europe and North America[12]. The mechanistic reasons for combining nattokinase with bromelain and nanocurcumin® are intuitive — each component has independent literature supporting fibrinolytic, antiplatelet, antioxidant, and anti-inflammatory activity.

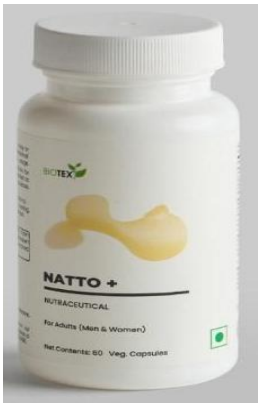


Figure 1: Biotex Natto+

Nattokinase: biochemistry, structural biology, and mechanism of action

Discovery and structural identity

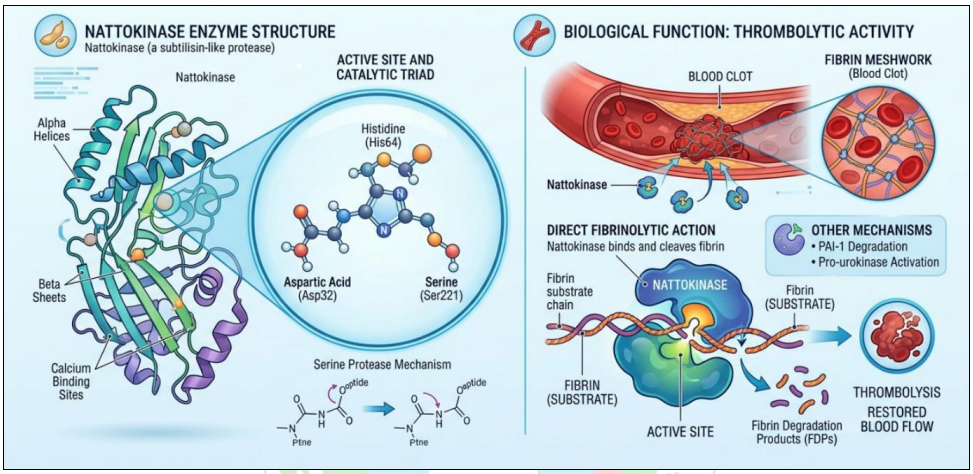


Figure 2: Nattokinase- Structure and biological function.

Nattokinase was originally isolated as a novel fibrinolytic enzyme exhibiting saline-extractable plasmin-equivalent activity of approximately 40 units per gram of wet natto by Sumi and colleagues from natto and reported in 1987. This is consistent with inhibition by di-isopropyl fluorophosphate, consistent with serine protease identity, and a molecular weight of approximately 20 kDa estimated by sodium dodecyl sulphate polyacrylamide gel electrophoresis[2]. After purification and chromatographic characterisation, Fujita and colleagues refined the molecular mass to 27,728 Da. They identified the mature polypeptide as a 275-amino-acid monomer which shows significant sequence similarity to the subtilisin family of bacterial serine proteases (Figure 2)[3]. Nucleotide sequencing of the corresponding aprN gene from Bacillus subtilis var. natto by Na I'm unable to check for AI detection directly. However, I can help you with tips on how to make your writing sound more natural or human-like. If you have a specific piece of text you want me to help with or edit, feel free to share it! Amura and colleagues confirmed that nattokinase is subtilisin NAT. X-ray crystallographic analysis at 1.74 Å resolution has shown that nattokinase is three-dimensionally similar to subtilisin E. It shares the canonical Asp32, His64, and Ser221 catalytic triad found in clan SB family S8 serine proteases. Despite this close structural relationship with other subtilisins, nattokinase has a unique preference for fibrin as a substrate. This feature supports its use as an oral fibrinolytic agent[1].

Direct fibrinolytic activity

Nattokinase directly cleaves fibrin without activating the plasminogen system, distinguishing it mechanistically from tissue-type plasminogen activator (t-PA), urokinase, and streptokinase, which all act through plasminogen conversion.[7,9]. In vitro studies have shown that both α- and β-chains of fibrin undergo dose-dependent proteolysis, with cross-linked fibrin being surprisingly susceptible to nattokinase, which exhibits greater fibrinolytic activity than plasmin. In a rat model of carotid artery thrombosis, intravenous nattokinase restored blood flow to about 62% of baseline, compared to only 16% for plasmin. Comparative studies suggest that nattokinase inhibits thrombus formation by over 90% at 75 mg/kg, with a safety margin of 4.0, which can increase to 8.0 when combined with low-dose dexamethasone. (Figure 3)[18].

Indirect fibrinolytic potentiation: PAI-1 inactivation and t-PA release

Arguably the most mechanistically important molecular target of nattokinase is plasminogen activator inhibitor-1. It is the principal physiological inhibitor of both t-PA and urokinase and the dominant determinant of net endogenous fibrinolytic capacity in hypercoagulable states[19]. Urano and colleagues demonstrated that subtilisin NAT cleaves active PAI-1 at its reactive centre between Arg346 and Met347 and inactivates it with a half-maximal effective concentration of

approximately 0.1 nM *in vitro*[19]. As PAI-1 is markedly elevated in patients with metabolic syndrome, type 2 diabetes, obesity, and atherothrombotic phenotypes, its inactivation produces net upregulation of endogenous fibrinolysis without overt systemic anticoagulation[7]. Complementing this mechanism, Yatagai and colleagues demonstrated that heat-inactivated nattokinase can still stimulate an approximately 20-fold increase in t-PA release from cultured human umbilical vein endothelial cells. This suggests that the non-enzymatic parts of the molecule maintain their ability to signal in endothelial cells.[20]. Subsequent work by Ji and colleagues has identified roles for JAK1–STAT1 signalling and intracellular cyclic adenosine monophosphate (cAMP) elevation in the vascular and anti-apoptotic effects of nattokinase[21].

The integrated human haemostatic effect of these mechanisms was elegantly demonstrated by Kurosawa and colleagues in a double-blind crossover study of 12 healthy young men. In this research, a single oral dose of 2,000 FU of nattokinase resulted in statistically significant increases in D-dimer levels at 6 and 8 hours, along with rises in fibrin and fibrinogen degradation products at 4 hours. It also demonstrated an enhancement in antithrombin activity at 2 and 4 hours, as well as a prolongation of the activated partial thromboplastin time, while factor VIII activity showed a decline[22]. Critically, every parameter remained within normal physiological ranges, consistent with fibrinolytic potentiation rather than systemic anticoagulation. This gives a pharmacological signature that distinguishes nattokinase from prescription anticoagulants and that supports its safety in non-anticoagulated populations (Figure 3) [8,22].

Antiplatelet activity

Aside from its impact on the fibrinolytic cascade, nattokinase also exhibits direct antiplatelet activity, thereby enhancing its overall antithrombotic properties[23].In comprehensive in vitro and in vivo studies, Jang and his colleagues demonstrated that nattokinase inhibits rabbit platelet aggregation induced by both collagen and thrombin in a concentration-dependent manner. They found that nattokinase reduces thromboxane B2 formation from collagen-activated platelets. Thromboxane B2 is the stable metabolite of thromboxane A2, a potent platelet activator and vasoconstrictor. Additionally, nattokinase protects against ferric chloride-induced carotid thrombosis in rats, with an efficacy comparable to that of aspirin at a dosage of 30 mg/kg[23]. The mechanism appears to involve elevation of intracellular cAMP and attenuation of agonist-induced calcium transients within platelets[23]. Zhang and colleagues have additionally shown that nattokinase is a heparin-binding protein with an apparent affinity of approximately 250 nM and a chain-length-dependent interaction. This interaction requires at least a hexasaccharide of heparin, suggesting complex modulation of heparin–antithrombin interactions that may shape its in vivo anticoagulant phenotype (figure 3)[24].

Renin–angiotensin system modulation and antihypertensive activity

The antihypertensive activity of nattokinase appears to derive from at least two parallel molecular pathways. One is mediated by intact enzyme and the other by enzymatic fragments generated during gastric and intestinal hydrolysis[25]. Intact nattokinase displays mixed-type inhibition of angiotensin-converting enzyme (ACE) in vitro. But heat-induced fragmentation markedly increases this potency by liberating short ACE-inhibitory dipeptides, notably leucine–tyrosine (Leu-Tyr) and phenylalanine–tyrosine (Phe-Tyr), identifiable by high-performance liquid chromatography–mass spectrometry[26]. Fujita and colleagues studies on spontaneously hypertensive rats showed that intact nattokinase lowered blood pressure principally through plasma fibrinogen depletion without affecting renin, ACE, or angiotensin II concentrations. In contrast, orally administered enzymatic fragments lowered blood pressure through suppression of the renin–angiotensin system[25]. This dual-pathway model is consistent with the human observation that plasma renin activity decreases with chronic nattokinase supplementation- documented in the Kim randomised controlled trial (Figure 3)[4].

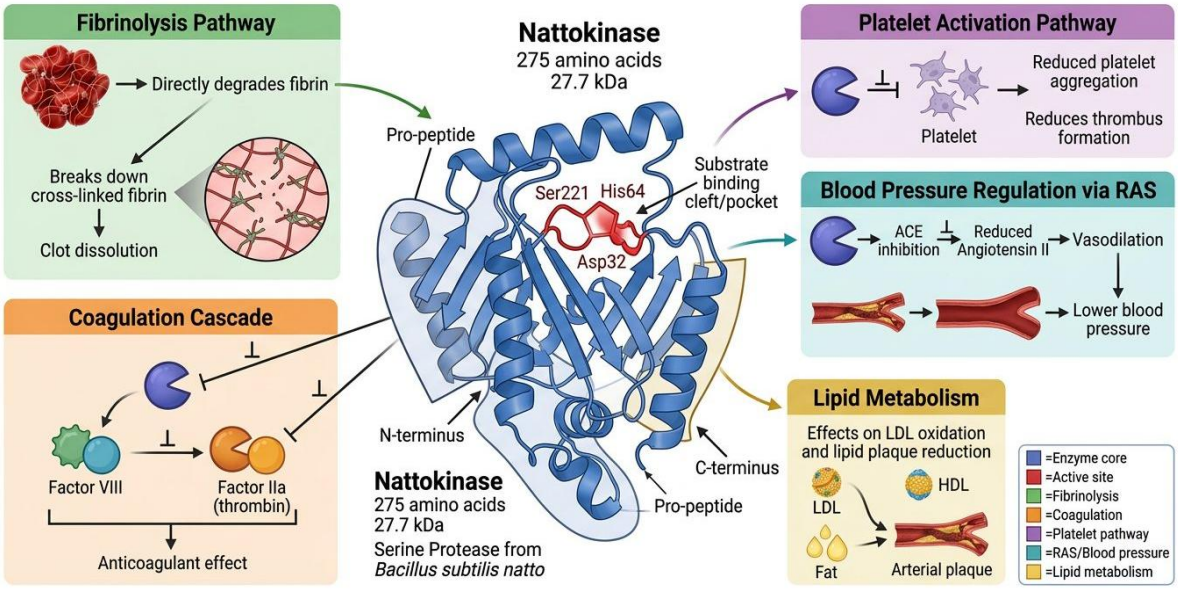


Figure 3: Nattokinase and its application in cardiovascular diseases.

Oral bioavailability and pharmacokinetics

The oral bioavailability of nattokinase has been the most debated aspect of its pharmacology, which is to be expected for a 27.7 kDa polypeptide, as the intact absorption through the mucosal membrane is theoretically unlikely[9]. In a study involving rats, Fujita and his team found that intact nattokinase was present in the plasma 3 to 5 hours following intraduodenal administration. They noted the degradation of circulating fibrinogen, which indicates that there is at least partial absorption of the active enzyme[17]. Feng and associates later showed, through experiments with Caco-2 cell monolayers and rat everted-gut sacs, that enterocytes internalise nattokinase via a mix of macropinocytosis, clathrin-mediated endocytosis, and caveolae-mediated endocytosis—vesicular pathways that align with the uptake of the partially intact enzyme[27]. In the only published human pharmacokinetic study, an enzyme-linked immunosorbent assay-based method detected immunoreactive nattokinase peaking in serum approximately 13.3 ± 2.5 h after a single 2,000 FU oral dose in 11 healthy adults[28].

These results are tempered by two significant cautions. First, the European Food Safety Authority's 2016 opinion on the NSK-SD® raw material found that the submitted absorption, distribution, metabolism, and excretion data did not allow for firm conclusions regarding the systemic absorption of either active nattokinase or functional metabolites. Second, the Ero assay could not discriminate intact enzyme from immunoreactive peptide fragments[12,28]. The current synthesis is that intact enzyme contributes at low bioavailability and that bioactive absorbed peptide fragments — including the ACE-inhibitory dipeptides identified by Murakami and colleagues — also contribute to the integrated pharmacological effect observed in humans[26,27]. The subtilisin fold's resistance to acid denaturation, along with the use of HPMC or enteric-coated capsules, both play a role in ensuring the delivery of biologically significant activity to the absorptive surface of the duodenum.[29].

Mechanistic rationale for the co-formulants in Biotex Natto+

Bromelain from pineapple extract

Bromelain is a complex of cysteine proteases extracted predominantly from the stem and fruit of *Ananas comosus*, comprising stem bromelain, fruit bromelain, ananain, and several associated peptidases, glycoproteins, and protease inhibitors[30]. It has been used in European medical practice as an oral anti-inflammatory and adjunct antithrombotic agent for several decades. This is supported by a literature documenting fibrinolytic, antiplatelet, anti-oedema, anti-inflammatory, and immunomodulatory activity in vitro and in animal models[31]. Mechanistically relevant to the cardiovascular positioning of Biotex Natto+, bromelain has been shown to enhance fibrinolysis through stimulation of plasminogen-to-plasmin conversion, inhibit adenosine diphosphate and thrombin-induced platelet aggregation, reduce circulating fibrinogen, and modulate inflammatory cytokine signalling[30,32].

The bioavailability of orally administered bromelain is supported by both pharmacokinetic and pharmacodynamic observations. After oral dosing, intact functional bromelain has been detected in human plasma, and clinically meaningful biological effects have been observed at doses of 200 to 2,000 mg per day - within the range delivered by typical multi-ingredient formulations[31]. In Biotex Natto+, the 250 mg per capsule dose of pineapple extract is consistent with the lower end of this range. It would be expected to contribute additive proteolytic and anti-inflammatory effects to the predominant nattokinase signal rather than to drive the cardiovascular activity of the formulation independently[31,32].

Standardised nanocurcumin®

Curcumin, the principal yellow polyphenol of *Curcuma longa* rhizome, is one of the most extensively studied natural products in cardiovascular pharmacology. The mechanistic effects of Curcumin include antioxidant, anti-inflammatory, antiplatelet, anti-fibrotic, and endothelial-modulatory pathways[33]. Curcumin's significance in cardiovascular health is backed by mechanistic studies and limited clinical evidence that suggest it reduces oxidative stress, diminishes inflammatory signalling driven by nuclear factor-kappa B, and inhibits platelet activation mediated by glycoprotein VI by interfering with spleen tyrosine kinase activity and subsequent phosphorylation of phospholipase Cγ2. There are also modest enhancements in endothelial function and beneficial changes in lipid profiles under certain conditions[34,35].

The principal pharmacokinetic limitation of native curcumin is poor aqueous solubility, rapid intestinal and hepatic glucuronidation and sulphation, and extensive first-pass metabolism. These together produce systemic concentrations far below the in vitro effective range achievable with simple oral dosing[36]. Numerous strategies to enhance bioavailability have been created, such as the co-administration of piperine, lipid-based formulations, phospholipid complexes, and nanoparticle dispersions. From all these formulation strategies, the post-digestive solubility of the curcumin payload has been recognised as the primary factor influencing oral bioavailability[37]. Nanocurcumin®, a class of submicron particulate dispersions of curcumin, achieves substantially greater apparent oral bioavailability than crystalline curcumin and is therefore the more rational choice for inclusion in a multi-ingredient cardiovascular nutraceutical[36,37]. Additive antiplatelet, anti-inflammatory, and antioxidant activity is contributed by the mechanistic position of a 50 mg dose of standardised nanocurcumin® in Biotex Natto+ rather than to drive a primary lipid-lowering or fibrinolytic effect (Figure 4).

Mechanistic complementarity within Biotex Natto+

Considered as an integrated formulation, the three actives in Biotex Natto+ converge on a coherent set of cardiovascular targets: fibrinolytic enhancement (nattokinase, bromelain), antiplatelet activity (nattokinase, bromelain, curcumin), anti-inflammatory and endothelial modulation (curcumin, nattokinase), and renin–angiotensin system modulation (nattokinase)[9,31,33]. This mechanistic complementarity provides a plausible biological rationale for combination dosing. Even though the open empirical question — whether the combination produces additive or synergistic clinical effects relative to nattokinase monotherapy — has not been answered by published randomised trials of Biotex Natto+ specifically[8]. The established precedent for combination efficacy in this therapeutic category is evident with

nattokinase and red yeast rice. The addition of monacolin K-rich red yeast rice resulted in significant lipid reductions that nattokinase alone could not achieve[38,39].

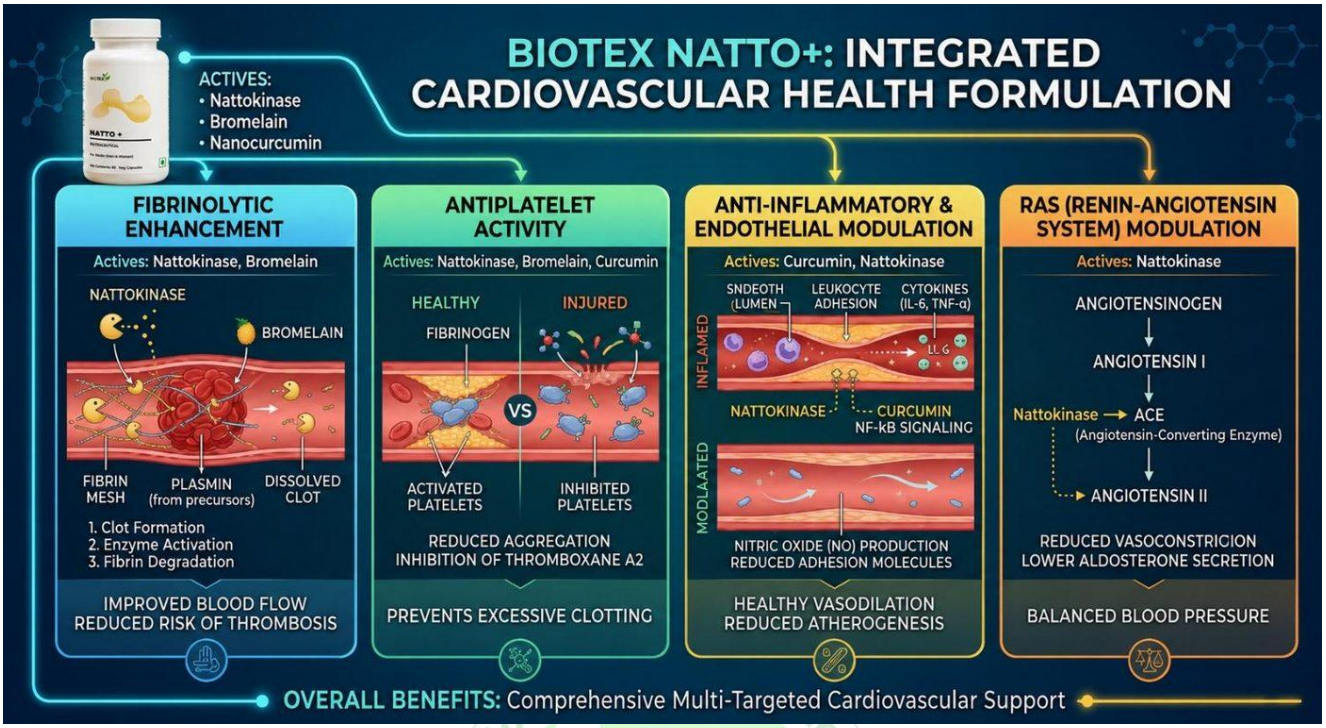


Figure 4: Biotex Natto+, an integrated approach to tackle cardiovascular health.

Clinical Evidence In Human Subjects

The clinical literature on nattokinase now comprises more than a dozen randomised controlled trials, several large open-label and observational studies, and a 2023 PROSPERO-registered meta-analysis[6]. The aggregate evidence supports modest reproducible effects on blood pressure, coagulation factors, and vascular imaging endpoints, with a smaller and more dose-dependent signal on lipid parameters[6,9]. The following subsections appraise the principal trials by endpoint domain.

Acute fibrinolytic and anticoagulant effects

The most rigorous human demonstration of acute biological activity after a single oral dose of nattokinase comes from the double-blind placebo-controlled crossover study of Kurosawa and colleagues. In this study, 12 healthy young men received either 2,000 FU of nattokinase or placebo and underwent serial coagulation and fibrinolytic assays over 8 h[22]. With all parameters remaining within normal physiological ranges, the study documented statistically significant increases in D-dimer and fibrin/fibrinogen degradation products, elevation of antithrombin activity, prolongation of activated partial thromboplastin time, and reduction of factor VIII activity [22]. These findings provide the clearest single-dose human evidence that an oral nattokinase capsule simultaneously enhances fibrinolysis and attenuates procoagulant activity without producing overt systemic anticoagulation[22].

Blood pressure

Blood pressure reduction is the best-replicated clinical endpoint for nattokinase across geographically and ethnically distinct cohorts[6,9]. The key randomised controlled trial by Kim and colleagues enrolled 86 Korean adults with baseline systolic blood pressure 130 to 159 mmHg, among them 73 completed the 8-week protocol receiving either 2,000 FU per day of nattokinase or placebo[4]. Compared with placebo, nattokinase produced a net reduction in systolic blood pressure of −5.55 mmHg (95% confidence interval, −10.5 to −0.57; $p < 0.05$) and diastolic blood pressure of −2.84 mmHg (95% confidence interval, −5.33 to −0.33; $p < 0.05$). This was accompanied by a statistically significant reduction in plasma renin activity of −1.17 ng/mL/h, providing mechanistic support for the haemodynamic effect[4].

These findings were replicated in the multicentre North American randomised controlled trial of Jensen and colleagues, in which 79 hypertensive adults received 100 mg per day of standardised nattokinase (NSK-SD®) or placebo for 8 weeks[40]. The active treatment group observed overall decreases in diastolic blood pressure by around 3 mmHg, with a reduction of 5 mmHg noted in the male subgroup. There were also statistically significant declines in von Willebrand factor, a marker of vascular risk, primarily among female participants, indicating that there are sex-specific factors in the haemostatic and endothelial responses that require further exploration of their mechanisms[40]. Earlier observational data from Hitosugi and colleagues had similarly reported modest blood pressure reductions in patients with established lifestyle diseases, providing real-world contextual support for the trial findings[41].

A systematic review and meta-analysis conducted by Li and colleagues in 2023, which is registered with PROSPERO and involved six randomised controlled trials with a total of 546 participants, assessed the effects of nattokinase on blood pressure. The findings revealed an average reduction in systolic blood pressure of −3.45 mmHg and a diastolic

reduction of −2.32 mmHg, both statistically significant, with no indication of serious adverse events[6]. The effect sizes observed are clinically significant as supplementary treatments for pre-hypertension and stage 1 hypertension, but they do not reach the level typically associated with first-line antihypertensive medications. This highlights that nattokinase should be considered an addition to, rather than a substitute for, established blood pressure management practices[6,8].

Coagulation factors and thrombotic biomarkers

The chronic coagulation effects of nattokinase have been most thoroughly characterised by Hsia and colleagues. They have done a 2-month open-label self-controlled study of 45 subjects across three risk strata — healthy adults, adults with cardiovascular risk factors, and dialysis patients. They collected 4,000 FU per day, recorded statistically significant reductions in plasma fibrinogen of 7 to 10%, factor VII of 7 to 14%, and factor VIII of 17 to 19%, without change in lipid parameters and notable adverse events[5]. Yoo and colleagues, in randomly controlled trial in non-diabetic hypercholesterolaemic adults receiving nattokinase for 8 weeks, reported statistically significant prolongation of collagen–epinephrine closure time, prothrombin time, and activated partial thromboplastin time. This provides convergent evidence of a multi-node, modest shift away from a prothrombotic state at standard doses[42]. Considering these studies indicate that chronic nattokinase administration produces a coherent prothrombolytic phenotype detectable across complementary haemostatic assays (Figure 5) [8,9].

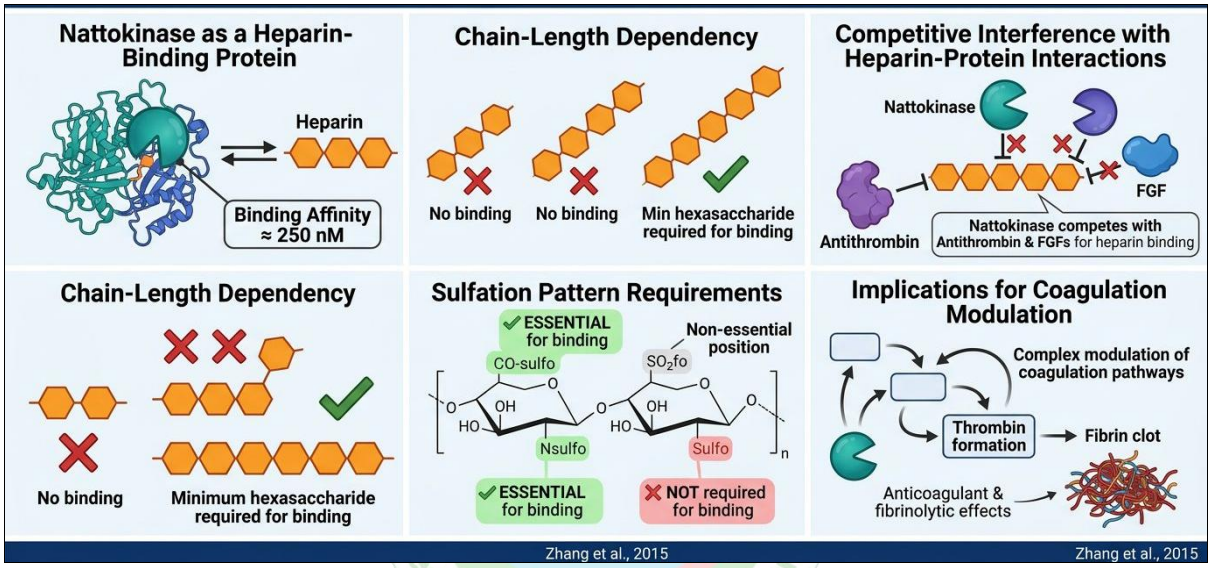


Figure 5: Nattokinase and its application in the coagulation cascade mechanism

Atherosclerosis and vascular imaging endpoints

Clinical findings for nattokinase most strikingly concern atherosclerotic plaque burden and carotid intima-media thickness[43,44]. Ren and colleagues randomised 76 patients with carotid atherosclerosis and hyperlipidaemia to receive either nattokinase 6,000 FU per day or simvastatin 20 mg per day for 26 weeks. They reported a 36.6% reduction in carotid plaque size in the nattokinase arm compared with 11.5% in the simvastatin arm and a reduction of common-carotid intima-media thickness from 1.13 ± 0.12 mm to 1.01 ± 0.11 mm[43]. Plaque regression in the nattokinase arm did not correlate with lipid changes, supporting the hypothesis that vascular-wall and fibrinolytic mechanisms — rather than lipid lowering — are the dominant drivers of atherosclerosis modification by nattokinase[43].

The parallel arm of the Chen study that administered 3,600 FU per day was found to be ineffective for both lipids and atherosclerosis. This finding led the authors to suggest that the previously used dose of 2,000 FU per day in earlier studies is considerably inadequate for modifying atherosclerosis. This dose-response observation has direct implications for the labelling of multi-ingredient products like Biotex Natto+[44]. The main limitation of the Chen study is that it uses a retrospective controlled design instead of a prospective randomisation. This makes the effect estimates vulnerable to selection and co-intervention bias, even though the dataset is large[44].

A rigorously designed long-duration trial is the Nattokinase Atherothrombotic Prevention Study (NAPS) reported by Hodis and colleagues. This study is on 265 adults without clinical cardiovascular disease who received nattokinase 2,000 FU per day or placebo for a median of three years[45]. Concerning the progression of carotid intima-media thickness, arterial stiffness, blood pressure, blood rheology, markers of coagulation and fibrinolysis, or systemic inflammation, no notable differences were found between nattokinase and a placebo [45]. The differences observed between NAPS and earlier successful trials can primarily be explained by three factors: the low-risk baseline group in NAPS, the administration of a daily dose of 2,000 FU, which the later Chen analysis indicates is below the threshold for atherosclerosis, and the lack of a documented hypercoagulable phenotype at the time participants entered the trial[44,45]. NAPS thus delineate the boundary of nattokinase's clinical utility without invalidating the positive findings in higher-risk, higher-dose, shorter-duration trials[8].

Lipid profile

The effects of nattokinase on lipid levels vary widely according to the available research. In a study by Yang and others, they found that taking nattokinase alone for six

months did not lead to any noticeable changes in lipid levels in adults with high cholesterol. When nattokinase was combined with red yeast rice, participants saw a 15% reduction in triglycerides, a 25% drop in total cholesterol, and a significant 41% decrease in low-density lipoprotein (LDL) cholesterol[38]. The significant pharmacological driver of these lipid effects is the monacolin K content of red yeast rice, which is structurally and pharmacologically equivalent to lovastatin, so the result cannot be attributed to nattokinase alone[38]. In a 4-month randomised study by Liu and colleagues, a nattokinase–Monascus combination reduced total cholesterol by 0.52 mmol/L and low-density lipoprotein cholesterol by 0.43 mmol/L without changing triglycerides, HDL-C, or carotid intima-media thickness[39]. The 2023 meta-analysis by Li found that low doses of nattokinase alone often do not lead to noticeable changes in lipid levels. In the Chen 2022 study, some positive effects on lipids were seen with higher daily doses [6,44,46]. The most defensible interpretation is that nattokinase is not a lipid-lowering agent in its own right but exerts adjunctive lipid effects at higher doses or in combination with established hypolipidaemic agents[46].

Stroke, venous thromboembolism, and other cardiovascular endpoints

Beyond its effects on blood pressure and atherosclerosis, several smaller studies have looked at nattokinase for stroke recovery, preventing venous thromboembolism, and as a supplement in treating coronary artery disease[47]. The Nattospes study by Pham and colleagues reported improved Rankin, Orgogozo, and Barthel scores in 61 subacute ischaemic stroke patients who received adjunctive nattokinase over 60 days, but the open-label design and the use of a fixed-combination product limit the strength of inference[47]. A randomised controlled trial: The LONFLIT-FLITE trial by Cesarone and colleagues on 204 long-haul air travellers receiving Flite Tabs (a 150 mg pinokinase/nattokinase complex) or placebo. They reported zero deep vein thromboses in the active arm versus five (5.4%) in the placebo arm, providing the most striking product-specific evidence for venous thromboembolism prevention by an oral fibrinolytic complex[48]. Mechanistic studies in cerebral ischaemia models support neuroprotective potential through anti-inflammatory, anti-apoptotic, antioxidant, and microcirculatory mechanisms. But clinical translation in stroke prevention remains an emerging rather than established indication[49,50].

Real-world safety in vascular patients

Real-world safety data adds to findings from controlled trials. Gallelli and colleagues studied 153 patients, aged 22 to 92, with deep or superficial venous thrombosis or chronic venous insufficiency. These patients received 100 mg of nattokinase daily, either alone or along with fondaparinux or enoxaparin. They observed clinical improvements without any adverse drug reactions or interactions, as long as the international normalised ratio was monitored. This supports a positive safety profile for nattokinase in properly managed vascular patients[51].

Safety profile, adverse effects, and clinically relevant drug interactions

A reassuring aspect of nattokinase's safety profile is that throughout numerous randomised controlled trials, including the 1,062-participant Chen study, the enzyme has shown consistent tolerability, with no significant adverse effects linked to nattokinase observed at doses reaching up to 10,800 FU per day[6,44]. Toxicological assessment by Lampe and English reported that nattokinase derived from Bacillus subtilis var. natto was non-mutagenic and non-clastogenic in vitro and produced no adverse effects in 28-day and 90-day rodent toxicity studies. The European Food Safety Authority's 2016 novel-food opinion concluded that the NSK-SD® raw material is safe at doses up to 100 mg per day in healthy adults over 35 years of age, excluding pregnant and lactating women[12,52].

The qualifying component of the safety story relates to interaction with prescription antithrombotic agents and clinical scenarios in which haemostatic margin is narrow[53]. The published case-report literature contains genuine safety signals: cerebellar haemorrhage after combined nattokinase and aspirin use in a patient with cerebral microbleeds, fatal hemoperitoneum in an elderly woman taking nattokinase, and valve thrombosis after a patient replaced warfarin with nattokinase following mechanical aortic valve replacement[54,55]. These instances do not assess the overall risk to the population, but they lead to one clear clinical conclusion: nattokinase should be used carefully in situations where the risks of bleeding or thrombosis are elevated[53].

Appropriate contraindications and precautions include the concurrent use of warfarin, direct oral anticoagulants, heparin, aspirin, clopidogrel, or other antithrombotic medications (where monitored use with international normalised ratio assessment may be permissible, but unmonitored combination is not recommended). Caution is advised in cases of active bleeding, peptic ulcer disease, recent or upcoming surgeries, mechanical heart valves, a history of hemorrhagic stroke or cerebral microbleeds, and during pregnancy or breastfeeding, as there is limited direct safety data in these situations[53,54,56]. Mild gastrointestinal effects: bloating, nausea, and altered stool consistency have been reported idiosyncratically in clinical trials but are not a prominent or dose-limiting feature of the safety profile[8].

Regulatory landscape

The regulatory environment for nattokinase varies materially by jurisdiction[11,12].

a) In the United States, nattokinase is marketed under the Dietary Supplement Health and Education Act of 1994; most commercial products rely on self-affirmed Generally Recognised as Safe (GRAS) conclusions, and the FDA does not sanction disease-treatment claims for nattokinase supplements, with structure-and-function claims requiring the standard regulatory disclaimer[8].

b) In the European Union, the European Food Safety Authority's Panel on Dietetic Products, Nutrition and Allergies issued a formal novel-food opinion on fermented soybean extract NSK-SD® in 2016, concluding that it is safe at a limited intake, while explicitly noting that the submitted absorption, distribution, metabolism, and excretion data did not allow firm conclusions regarding systemic absorption of active enzyme or functional metabolites[12].

c) In Japan, where natto is a traditional food, nattokinase-containing products are marketed predominantly under the Foods with Function Claims notification system introduced in 2015 rather than as individually licensed Foods for Specified Health Uses[57].

d) In India, where Biotex Natto+ is manufactured and marketed, nutraceuticals are regulated by the Food Safety and Standards Authority of India under the Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2022, which expressly include nattokinase enzyme on the schedule of permitted nutraceutical ingredients[11]. Biotex Natto+ falls under this framework with accompanying expectations of good manufacturing practice compliance[10].

e) Canada: Nattokinase products carry Natural Product Numbers (NPNs) under the Natural Health Products regulation administered by Health Canada.

Limitations of the evidence base and priorities for future research

Several limitations qualify the present evidence base for nattokinase as a cardiovascular nutraceutical[8]. First, most published randomised controlled trials are small (typically under 100 participants) and of short duration (8 to 26 weeks). The studies focused on surrogate biomarkers and imaging endpoints rather than hard cardiovascular outcomes, and were conducted predominantly in East Asian populations[6,9]. The NAPS trial, though large and long, studied a low-risk population at a modest dose, limiting its generalisability in either direction[45]. There has yet to be a sufficiently powered randomised controlled trial assessing the impact of nattokinase supplementation on serious outcomes like myocardial infarction, ischemic stroke, venous thromboembolism, or overall mortality[8].

Second, pharmacokinetic uncertainty persists regarding the relative contribution of intact enzyme versus bioactive peptide fragments, the dose–response relationship, and inter-individual variability in absorption[27,28]. Third, Data on long-term safety beyond three years are scarce, and there is currently no systematic pharmacovigilance in place for monitoring spontaneous bleeding events in chronic users within existing registries[53]. Fourth, the clinical evidence base for multi-ingredient combinations of nattokinase with bromelain and curcumin – specifically the formulary class to which Biotex Natto+ belongs – is currently extrapolated from monotherapy trials of each component, with no published randomised controlled trial of the specific combination at issue[31,33].

Future research should focus on well-designed randomised controlled trials involving patients with hypertension and atherosclerosis, utilising specified imaging and definitive cardiovascular outcomes. It is also essential to conduct head-to-head comparisons of JNKA-certified standardised materials against non-certified alternatives to assess the clinical effects of variability in standardisation. Pharmacokinetic and pharmacodynamic studies involving interactions with warfarin and direct oral anticoagulants are necessary, alongside the use of validated biomarker panels for personalised dosing. Lastly, randomised trials should evaluate specific multi-ingredient combinations, such as the Biotex Natto+ blend of nattokinase, bromelain, and curcumin, to determine if their potential synergistic effects offer advantages over single therapies[8,56].

CONCLUSIONS

Nattokinase has progressed from a serendipitous fibrin-plate observation by Sumi in 1980 to one of the best-characterised oral fibrinolytic nutraceuticals in the contemporary cardiovascular pharmacology literature[2,9]. It combines direct fibrin degradation with PAI-1 inactivation, endothelial t-PA release, ACE inhibition through orally absorbed peptide fragments, and antiplatelet activity. A pleiotropic profile consistent with the integrated clinical fingerprint observed across more than a dozen randomised trials[19,20,23,26]. A clinically coherent body of randomised and meta-analytic evidence supports modest but reproducible reductions in blood pressure, fibrinogen and coagulation factors, carotid intima-media thickness, and plaque size at doses spanning 540mg per day, RDA recommended. This is offset by a clinically important but contextual bleeding-risk signal in patients on concurrent antithrombotics or with cerebral microangiopathy and by a single high-quality negative trial in a low-risk population[4,6,44,45].

Biotex Natto+ is conceptually well positioned within this landscape as a multi-ingredient formulation that combines nattokinase with bromelain and standardised nanocurcumin, potentially exploiting mechanistic synergies documented for each component in isolation[10,31,33]. The main opportunities for the manufacturer include clearly stating the fibrinolytic-unit potency of the nattokinase fraction, explicitly citing the dosage applied in key clinical studies, and funding clinical trials specific to the product to transform evidence related to the ingredient class into claims specific to the formulation[8]. For healthcare professionals like clinicians, dietitians, and pharmacists responding to inquiries about Biotex Natto+ and similar nattokinase combination products, the most reliable guidance currently available suggests that these products can be viewed as supplementary nutritional support for adults with pre-hypertension or stage 1 hypertension, particularly those who have documented carotid atherosclerosis. They may be used alongside lifestyle changes and statin medications, which might be beneficial for low-risk individuals looking for a mild pro-fibrinolytic effect, but caution and appropriate supervision are recommended for those on prescription anticoagulants or in surgical or obstetric situations where the risk of bleeding is higher[53,56].

Conflicts of interest and funding

No external funding was received for the preparation of this review. All product specifications were obtained from publicly accessible manufacturer materials, and all scientific claims are supported by peer-reviewed references verified at the time of writing.

Declarations

Conflict of Interest

The authors are affiliated with Biotex Life Solutions, the manufacturer of Biotex Natto+. Product specifications were obtained from publicly accessible manufacturer materials; all

scientific claims are supported by independent peer-reviewed literature.

Funding

No external funding was received for the preparation of this review. Internal support was provided by Biotex Life Solutions, which did not influence the evidence synthesis or conclusions.

Author Contributions

All authors contributed to the conception of the review, literature identification and appraisal, synthesis and interpretation of evidence, and manuscript drafting and critical revision. All authors approved the final version and agree to be accountable for the accuracy and integrity of the work.

Ethics Statement

Not applicable. This is a review article involving no new studies on human or animal subjects.

Use of Artificial Intelligence

Artificial intelligence tools were used for image illustration and proofreading. The authors verified all content and take full responsibility for the work.

Data Availability

Not applicable. All data discussed derive from the cited, publicly available published literature.

REFERENCES:

1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982-3021. doi:10.1016/j.jacc.2020.11.010
2. Sumi H, Hamada H, Tsushima H, Mihara H, Muraki H. A novel fibrinolytic enzyme (nattokinase) in the vegetable cheese natto: a typical and popular soybean food in the Japanese diet. *Experientia*. 1987;43(10):1110-1111. doi:10.1007/BF01956052
3. Fujita M, Nomura K, Hong K, Ito Y, Asada A, Nishimuro S. Purification and characterization of a strong fibrinolytic enzyme (nattokinase) in the vegetable cheese natto, a popular soybean fermented food in Japan. *Biochem Biophys Res Commun*. 1993;197(3):1340-1347. doi:10.1006/bbrc.1993.2624
4. Kim JY, Gum SN, Paik JK, et al. Effects of nattokinase on blood pressure: a randomized, controlled trial. *Hypertens Res*. 2008;31(8):1583-1588. doi:10.1291/hypres.31.1583
5. Hsia CH, Shen MC, Lin JS, et al. Nattokinase decreases plasma levels of fibrinogen, factor VII, and factor VIII in human subjects. *Nutr Res*. 2009;29(3):190-196. doi:10.1016/j.nutres.2009.01.009
6. Li X, Long J, Gao Q, et al. Nattokinase supplementation and cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials. *Rev Cardiovasc Med*. 2023;24(8):234. doi:10.31083/j.rcm2408234
7. Altaf F, Wu S, Kasim V. Role of fibrinolytic enzymes in anti-thrombosis therapy. *Front Mol Biosci*. 2021;8:680397. doi:10.3389/fmolb.2021.680397
8. Granito M, Alvarenga L, Ribeiro M, Lima V, Cardozo LFMF, Mafra D. Nattokinase as an adjuvant therapeutic strategy for non-communicable diseases: a review of fibrinolytic, antithrombotic, anti-inflammatory, and antioxidant effects. *Expert Rev Cardiovasc Ther*. 2024;22(10):565-574. doi:10.1080/14779072.2024.2416663
9. Chen H, McGowan EM, Ren N, et al. Nattokinase: a promising alternative in prevention and treatment of cardiovascular diseases. *Biomark Insights*. 2018;13:1177271918785130. doi:10.1177/1177271918785130
10. Biotex Life Solutions. Biotex Natto+: product information. Accessed May 26, 2026. https://shop.biotexlife.com/products/natto
11. Food Safety and Standards Authority of India. Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2022. Accessed May 26, 2026. https://fssai.gov.in
12. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Safety of fermented soybean extract NSK-SD as a novel food pursuant to Regulation (EC) No 258/97. *EFSA J*. 2016;14(9):4541. doi:10.2903/j.efsa.2016.4541
13. Nakamura T, Yamagata Y, Ichishima E. Nucleotide sequence of the subtilisin NAT gene, aprN, of Bacillus subtilis (natto). *Biosci Biotechnol Biochem*. 1992;56(11):1869-1871. doi:10.1271/bbb.56.1869
14. Pan X, Liang P, Teng L, et al. Study on molecular mechanisms of nattokinase in pharmacological action based on label-free liquid chromatography-tandem mass spectrometry. *Food Sci Nutr*. 2019;7(10):3185-3193. doi:10.1002/fsn3.1157
15. Sheng Y, Yang J, Wang C, Sun X, Yan L. Microbial nattokinase: from synthesis to potential application. *Food Funct*. 2023;14(6):2568-2585. doi:10.1039/d2fo03389e
16. Shah S, Patel J, Patel R. Nattokinase: armour against thrombosis. *J Adv Sci Res*. 2022;13(5):27-32. doi:10.55218/jasr.202213504
17. Fujita M, Hong K, Ito Y, et al. Transport of nattokinase across the rat intestinal tract. *Biol Pharm Bull*. 1995;18(9):1194-1196. doi:10.1248/bpb.18.1194
18. Guo H, Ban YH, Cha Y, et al. Comparative anti-thrombotic activity and haemorrhagic adverse effect of nattokinase and tissue-type plasminogen activator. *Food Sci Biotechnol*. 2019;28(5):1535-1542. doi:10.1007/s10068-019-00580-1
19. Urano T, Ihara H, Umemura K, et al. The profibrinolytic enzyme subtilisin NAT purified from Bacillus subtilis cleaves and inactivates plasminogen activator inhibitor type 1. *J Biol Chem*. 2001;276(27):24690-24696. doi:10.1074/jbc.M101751200
20. Yatagai C, Maruyama M, Kawahara T, Sumi H. Nattokinase-promoted tissue plasminogen activator release from human cells. *Pathophysiol Haemost Thromb*. 2009;36(5):227-232. doi:10.1159/000252817
21. Ji H, Yu L, Liu K, et al. Mechanisms of nattokinase in protection of cerebral ischemia. *Eur J Pharmacol*. 2014;745:144-151. doi:10.1016/j.ejphar.2014.10.024
22. Kurosawa Y, Nirengi S, Homma T, et al. A single dose of oral nattokinase potentiates thrombolysis and anti-coagulation profiles. *Sci Rep*. 2015;5:11601. doi:10.1038/srep11601
23. Jang JY, Kim TS, Cai J, et al. Nattokinase improves blood flow by inhibiting platelet aggregation and thrombus formation. *Lab Anim Res*. 2013;29(4):221-225. doi:10.5625/lar.2013.29.4.221
24. Zhang L, Jia S, Platt MO, Xu Y. Interactions between nattokinase and heparin/GAGs. *Glycoconj J*. 2015;32(9):695-702. doi:10.1007/s10719-015-9620-8
25. Fujita M, Ohnishi K, Takaoka S, Ogasawara K, Fukuyama R, Nakamuta H. Antihypertensive effects of continuous oral administration of nattokinase and its fragments in spontaneously hypertensive rats. *Biol Pharm Bull*. 2011;34(11):1696-1701. doi:10.1248/bpb.34.1696
26. Murakami K, Yamanaka N, Ohnishi K, Fukayama M, Yoshino M. Inhibition of angiotensin I converting enzyme by subtilisin NAT (nattokinase) in natto, a Japanese traditional fermented food. *Food Funct*. 2012;3(6):674-678. doi:10.1039/c2fo10245e
27. Feng H, Liu C, Liu Q, et al. Study on the transport and internalisation mechanism of dietary supplement nattokinase in the small intestine using animal and Caco-2 cell monolayer models. *Xenobiotica*. 2023;53(12):670-680. doi:10.1080/00498254.2023.2284249
28. Ero MP, Ng CM, Mihailovski T, Harvey NR, Lewis BH. A pilot study on the serum pharmacokinetics of nattokinase in humans following a single, oral, daily dose. *Altern Ther Health Med*. 2013;19(3):16-19.

29. Cai D, Zhu C, Chen S. Microbial production of nattokinase: current progress, challenge and prospect. *World J Microbiol Biotechnol*. 2017;33(5):84. doi:10.1007/s11274-017-2253-2

30. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. *Cell Mol Life Sci*. 2001;58(9):1234-1245. doi:10.1007/PL00000936

31. Pavan R, Jain S, Shraddha, Kumar A. Properties and therapeutic application of bromelain: a review. *Biotechnol Res Int*. 2012;2012:976203. doi:10.1155/2012/976203

32. Chobotova K, Vernallis AB, Majid FAA. Bromelain's activity and potential as an anti-cancer agent: current evidence and perspectives. *Cancer Lett*. 2010;290(2):148-156. doi:10.1016/j.canlet.2009.08.001

33. Hewlings SJ, Kalman DS. Curcumin: a review of its effects on human health. *Foods*. 2017;6(10):92. doi:10.3390/foods6100092

34. Wongcharoen W, Phrommintikul A. The protective role of curcumin in cardiovascular diseases. *Int J Cardiol*. 2009;133(2):145-151. doi:10.1016/j.ijcard.2009.01.073

35. Mayanglambam A, Dangelmaier CA, Thomas D, Damodar Reddy C, Daniel JL, Kunapuli SP. Curcumin inhibits GPVI-mediated platelet activation by interfering with the kinase activity of Syk and the subsequent activation of PLCγ2. *Platelets*. 2010;21(3):211-220. doi:10.3109/09537100903528269

36. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm*. 2007;4(6):807-818. doi:10.1021/mp700113r

37. Flory S, Sus N, Haas K, et al. Increasing post-digestive solubility of curcumin is the most successful strategy to improve its oral bioavailability: a randomized cross-over trial in healthy adults and in vitro bioaccessibility experiments. *Mol Nutr Food Res*. 2021;65(24):e2100613. doi:10.1002/mnfr.202100613

38. Yang NC, Chou CW, Chen CY, Hwang KL, Yang YC. Combined nattokinase with red yeast rice but not nattokinase alone has potent effects on blood lipids in human subjects with hyperlipidemia. *Asia Pac J Clin Nutr*. 2009;18(3):310-317.

39. Liu X, Zeng X, Mahe J, et al. The effect of nattokinase-Monascus supplements on dyslipidemia: a four-month randomized, double-blind, placebo-controlled clinical trial. *Nutrients*. 2023;15(19):4239. doi:10.3390/nu15194239

40. Jensen GS, Lenninger M, Ero MP, Benson KF. 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. *Integr Blood Press Control*. 2016;9:95-104. doi:10.2147/IBPC.S99553

41. Hitosugi M, Hamada K, Misaka K. Effects of Bacillus natto products on blood pressure in patients with lifestyle diseases. *J Hypertens Open Access*. 2013;4(3):135. doi:10.4172/2167-1095.1000135

42. Yoo HJ, Kim M, Kim M, et al. The effects of nattokinase supplementation on collagen-epinephrine closure time, prothrombin time and activated partial thromboplastin time in nondiabetic and hypercholesterolemic subjects. *Food Funct*. 2019;10(5):2888-2893. doi:10.1039/c8fo02324g

43. Ren NN, Chen HJ, Li Y, McGowan GW, Lin YG. A clinical study on the effect of nattokinase on carotid artery atherosclerosis and hyperlipidaemia. *Zhonghua Yi Xue Za Zhi*. 2017;97(26):2038-2042. doi:10.3760/cma.j.issn.0376-2491.2017.26.005

44. Chen H, Chen J, Zhang F, et al. Effective management of atherosclerosis progression and hyperlipidemia with nattokinase: a clinical study with 1,062 participants. *Front Cardiovasc Med*. 2022;9:964977. doi:10.3389/fcvm.2022.964977

45. Hodis HN, Mack WJ, Meiselman HJ, et al. Nattokinase atherothrombotic prevention study: a randomized controlled trial. *Clin Hemorheol Microcirc*. 2021;78(4):339-353. doi:10.3233/CH-211147

46. Wei C, Cai R, Song Y, Liu X, Xu HL. Research progress of nattokinase in reducing blood lipid. *Nutrients*. 2025;17(11):1784. doi:10.3390/nu17111784

47. Pham PT, Han B, Hoang BX. Nattospes as effective and safe functional supplements in management of stroke. *J Med Food*. 2020;23(8):879-885. doi:10.1089/jmf.2019.0183

48. Cesarone MR, Belcaro G, Nicolaides AN, et al. Prevention of venous thrombosis in long-haul flights with Flite Tabs: the LONFLIT-FLITE randomized, controlled trial. *Angiology*. 2003;54(5):531-539. doi:10.1177/000331970305400502

49. Yang XY, Wang SL, Xue WC, et al. Nattokinase's neuroprotective mechanisms in ischemic stroke: targeting inflammation, oxidative stress, and coagulation. *Antioxid Redox Signal*. 2024;42(4-6):228-248. doi:10.1089/ars.2023.0527

50. Mahakalakar N, Mohariya G, Taksande B, Kotagale N, Umekar M, Vinchurney M. Nattokinase as a potential therapeutic agent for preventing blood-brain barrier dysfunction in neurodegenerative disorders. *Brain Res*. 2024;1849:149352. doi:10.1016/j.brainres.2024.149352

51. Gallelli G, Di Mizio G, Palleria C, et al. Data recorded in real life support the safety of nattokinase in patients with vascular diseases. *Nutrients*. 2021;13(6):2031. doi:10.3390/nu13062031

52. Lampe BJ, English JC. Toxicological assessment of nattokinase derived from Bacillus subtilis var. natto. *Food Chem Toxicol*. 2016;88:87-99. doi:10.1016/j.fct.2016.01.001

53. Memorial Sloan Kettering Cancer Center. Nattokinase: about herbs. Accessed May 26, 2026. https://www.mskcc.org/cancer-care/integrative-medicine/herbs/nattokinase

54. Chang YY, Liu JS, Lai SL, Wu HS, Lan MY. Cerebellar hemorrhage provoked by combined use of nattokinase and aspirin in a patient with cerebral microbleeds. *Intern Med*. 2008;47(5):467-469. doi:10.2169/internalmedicine.47.0620

55. Dobre MZ, Virgolici B, Doicin IC, Vîrgolici H, Stanescu-Spinu II. Navigating the effects of anti-atherosclerotic supplements and acknowledging associated bleeding risks. *Int J Mol Sci*. 2025;26(20):10183. doi:10.3390/ijms262010183

56. Muric M, Nikolic M, Todorovic A, Jakovljevic V, Vucicevic K. Comparative cardioprotective effectiveness: NOACs vs nattokinase-bridging basic research to clinical findings. *Biomolecules*. 2024;14(8):956. doi:10.3390/biom14080956

57. Afzaal M, Saeed F, Islam F, et al. Nutritional health perspective of natto: a critical review. *Biochem Res Int*. 2022;2022:5863887. doi:10.1155/2022/5863887