

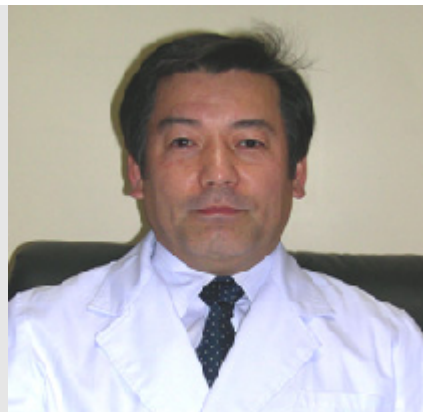
Purified Natto Culture Filtrate “NKCP” Decreases Risk of Thrombus Formation

NKCP regulates the balance of blood coagulation/fibrinolysis and is effective at preventing thrombosis.

Cardiac and cerebral vascular disorders account for a large percentage of the causes of death in Japanese people, and arteriosclerosis-induced thrombus formation is an important factor for these diseases. Natto bacillus culture is attracting attention as a functional food that can reduce the risk of thrombus formation.

“NKCP,” produced and sold by Daiwa Pharmaceutical Co., Ltd. has been subject to many studies from a range of viewpoints, and data on its efficacy and safety has been gathered. Notably, the effect on the blood coagulation/fibrinolysis system in humans has been studied.

Here, Dr Kazutoshi Kaketani of Hanzomon Gastrointestinal Clinic, who conducted this study, outlines the results of the study and describes how “NKCP” is used as a functional food.



Dr Kazutoshi Kaketani:

Born in Oita Prefecture in 1958. Graduated from Miyazaki Medical College in 1982. Received a PhD for the study of gastrointestinal carcinoma from Oita Medical University in 1990. Studied gastrointestinal endoscopy under Professor Hiromi Shinya at Albert Einstein College of Medicine in the U.S.A., and completed his fellowship.

Dr Kaketani is the director of Hanzomon Gastrointestinal Clinic, a visiting adviser for the Shinya Clinic in New York, and a councillor of the Japan Society for Endoscopic Surgery.

Significant difference between ELT and t-PA found
Hints of increased fibrinolytic activity

First, can you tell me the background to your interest in “NKCP”?

Kaketani: I am a gastrointestinal specialist, and I have examined over 100,000 patients using endoscopy. I have also treated many cancer patients, but very many of them died of

myocardial infarction or cerebral strokes after the cancer had been cured, and I wanted to do something about this.

The three major causes of death in Japanese people are cancer, cerebral strokes, and myocardial infarctions. The two diseases other than cancer are both triggered by arteriosclerosis. This made me pay attention to “NKCP,” which is expected to have a positive effect on blood and blood vessels.

You have studied the effect of “NKCP” on the blood coagulation/fibrinolysis system in humans. Can you give me a summary of the study?

Kaketani: We conducted two studies involving continuous administration over two weeks in 28 adults and chronic administration over two months in 23 adults. The dose was 250 mg/day in both studies, and laboratory tests, mainly consisting of haematology examinations and medical examinations, were performed before and after the study. In the chronic administration study, changes in subjective symptoms such as headaches, shoulder stiffness, and dizziness were also studied.

What were the results of measurement for the different parameters for blood coagulation/fibrinolysis?

Kaketani: In the two-week administration study, the ELT (euglobulin lysis time) was significantly shortened, from 9.8 ± 2.0 hr before administration, to 8.4 ± 1.7 hr afterwards, which corresponds to a 10.1% reduction on average. In the two-month administration study, the ELT was shortened but the level of t-PA (tissue plasminogen activator) increased (Table 1).

Table 1 Changes in fibrinolysis/coagulation parameters due to the administration of NKCP (in 23 subjects)

Parameter	Normal value	Pre- administration value	1 Month	2 Months
ELT ¹⁾	6-12 hrs.	9.0 ± 1.3	$8.1 \pm 1.5^{**}$	$8.0 \pm 1.5^{**}$
t-PA ²⁾	≤ 10 ng/mL	5.4 ± 2.6	5.8 ± 2.8	$6.4 \pm 2.2^*$
FDP ³⁾	≤ 4 μ g/mL	3.0 ± 0.7	2.0 ± 0.6	$3.0 \pm 0.7^*$

Data are expressed as mean values \pm standard deviation. A test using Duncan's multiple comparison showed a significant difference at significance levels of 5% (*) and 1% (**).

- 1) The upper measurement limit was 12 hours.
- 2) The lower measurement limit was 1.5 ng/ml.
- 3) The lower measurement limit was 2 μ g/ml.

The mechanism of this process may involve other factors and remains to be studied, but these studies certainly suggest that “NKCP” increases fibrinolytic activity.

What were the improvements in the subjective symptoms?

Kaketani: There were particularly noticeable improvements in shoulder stiffness (Table 2). The increased fibrinolytic activity may have improved local circulation in the muscles and surrounding tissue. I feel it will be necessary to study the correlation between the blood flow rate and blood viscosity, and the subjective symptoms at a future date.

Table 2 Changes in subjective symptoms due to the administration of NKCP

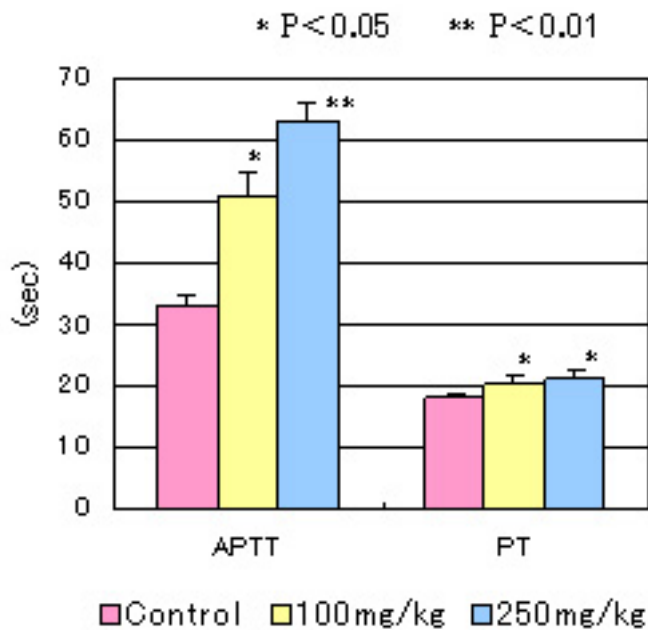
Symptom	Severity	Pre- administration	1 Month	2 Months
Headache	Severe	1	1	1
	Moderate	7	3	4
	No symptom (including mild headache)	15	16	16
	Remarkable improvement	—	3	2
	Shirley-Williams multiple test	—	N.S.	N.S.
Shoulder stiffness	Severe	5	1	1
	Moderate	10	9	10
	No symptom (including mild shoulder stiffness)	8	9	11
	Remarkable improvement	—	4	1
	Shirley-Williams multiple test	—	P<0.05	P<0.05
Dizziness	Severe	0	0	0
	Moderate	6	4	4
	No symptom (including mild dizziness)	17	18	18
	Remarkable improvement	—	1	1
	Shirley-Williams multiple test	—	N.S.	N.S.

Data is expressed as a number of patients. Significant differences were tested using multiple comparison. N.S. means no significant difference. p<0.05 means a significant difference at a significance level of 5%.

How do you rate the results of the study as a whole?

Kaketani: We were unable to obtain data on inhibited blood coagulation in the studies. However, experiments on rats showed a significant difference in ATPP (activated partial thromboplastin time and PT (prothrombin time), proving that blood coagulation was prolonged (Figure 1).

Figure 1
The inhibition of thrombus formation in rats due to the administration of NKCP



Platelets play a very important role in the early stage of thrombus formation. As “NKCP” has no effect on platelets, a complete demonstration would be difficult, but it is likely that another action of “NKCP” is involved in the inhibition of thrombus formation.

Achieving standards by identifying active ingredients and establishing a determination method

What type of people should take “NKCP”?

Kaketani: “NKCP” can be recommended to people with a risk of arteriosclerosis such as hyperlipidemia, hypertension, and diabetes mellitus, and those shown in a medical check-up to have an increased arteriosclerosis index. It is particularly suited to people with mild angina pectoris symptoms, but who do not appear to have abnormalities in an examination.

What do you emphasise to patients taking “NKCP”?

Kaketani: I emphasise that the effects will only last if they continue to take it. As the effect of “NKCP” is essentially independent of the amount ingested, I advise them to think of it as a food which supplements a deficiency in their diet.

What do you think about the requirements of functional foods?

Kaketani: A functional food is a food, and thus the first requirement is safety. It is right that efficacy is not made the first priority.

“NKCP” showed no problems in a toxicity study involving large doses, meaning it has a high level of safety. The mechanism of its action has been clarified to some extent, which also ensures that it is safe.

A determination method for “NKCP” has been established.

Kaketani: Bacillopeptidase F, a serinprotease, has been identified as the active ingredient of "NKCP," and a determination method has been established. As functional foods have the problem that the level of active ingredient is different for different lots, this standardization is a major achievement. Standardization is an important factor in guaranteeing the safety of functional foods.

The ability to decrease the risk of thrombosis suggests a range of possibilities in preventing disease.

How do you think "NKCP" could be useful in the future?

Kaketani: Based on the results of this study and previous results, I think that “NKCP” could be useful in preventing deep-vein thrombosis caused by lifestyle-related diseases. It also shows promise as a means of preventing economy-class syndrome and thrombosis after surgery or delivery. I want to emphasise that it inhibits thrombus formation but does not promote bleeding.

I also think that it will be effective combined with anti-platelet agents. I have actually combined these in many cases, because the combination has a low risk of interaction and is likely to increase the effects. “NKCP” is not a substitute for anti-platelet agents but it may decrease the frequency at which they must be given.

What remains to be studied?

Kaketani: At present, we believe that “NKCP” regulates the balance of blood coagulation and fibrinolysis and decreases the risk of arteriosclerosis. In the end, a long-term study will be necessary, and for example, if it is possible to analyse the incidence of events such as ischemic heart disorders, cerebral stroke, and cerebral infarction for groups taking "NKCP" and groups who are not, we will be able to obtain valuable data on its usefulness.

Thank you very much.

Address inquiries and requests for information about “NKCP” to:

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