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## ANALYSIS OF MAIN COMPONENTS AND PROSPECTS OF NATTO

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The word “natto” originated from Japan, which was known as stinky bean, salt bean or silk bean in Chinese folk. Natto contains multiple functional components, including

nattokinase, soybean isoflavone,  $\gamma$ -polyglutamic acid, vitamin K<sub>2</sub>, biogenic amines, SOD, small-molecule polypeptide, which has good preventive and curative effects for many diseases, such as cardiovascular and cerebrovascular diseases, hyperlipidemia, hypertension, menopausal symptoms and hyp immunity. Along with the aging population in the world and China, it is urgent to improve the quality of life. It is necessary to enhance the understanding of natto-related knowledge, expand propaganda power, accept natto consciously and eat natto frequently, which is good for our health and helps our country to build a healthy and harmonious society. This review will describe the development, components, functions and prospects of natto, which help us to offer theoretical basis for promoting natto industry.

## Natto, Nattokinase, Cardiovascular and Cerebrovascular

مقدمة

temple. Because the kitchen of the temple was called “豆腐”, the fermented soybean was called “豆豉”. At that time, natto was an important source of nutrition for vegetarian monks and was the imperial nutrition for Japanese royal families, nobilities and warriors. After Meiji Restoration in Japan, natto gradually flowed out from temple and royal family to normal Japanese people. In 1980, a Japanese researcher, Dr. Hiroyuki Sumi, accomplished the famous “2:30 pm experiment” in the laboratory of the University of Chicago in the United States [9]. He found that there was an enzyme in mucus thread that could dissolve thrombus, and named nattokinase. After that, with the development of refrigeration technology, natto had changed from workshop-type production to factory-type production. In 1983, Japan formulated the industry standard of natto. In 1992, the 7<sup>th</sup> Japanese natto festival was made up in July 10 representing “豆腐” and 10 representing “豆豉” in Japanese. Since 1996, when Japanese government has advocated people to eat natto, people’s height and life-span have been greatly improved. Natto is regarded as “the best healthy food in the world” in Japanese. Recently, WHO released the *food-Natto traditional rarest thebook*, 2018. In this report, nothing is in *Statistics Health World* latest report, more concerned than the life-span ranking list. Japanese average life span has been the highest for 20 years, reaching 84 on average, of which the life-span of the female is 87, and that of the male is 81. However, the Chinese life-span is only 76 years old. In addition to Japanese unique geographic environment, it has a great matter with the Japanese always eating traditional fermented food “natto”. This is the reason why Japan can become the longest-lived country in the world.

## 2.2. Health Care Functions and Main Components of Natto

In addition to its unique flavor and convenient production, natto also has a variety of nutritional and health care functions, for example, -dissolving blood-clot, reducing blood pressure, anti-bacteria, anti tumor, preventing osteoporosis, promoting gastrointestinal health, etc. -polyglutamic acid,  $\gamma$ -Natto contains nattokinase, soybean isoflavone, -, biogenic amines, superoxide dismutase (SOD), small- $\gamma$ -vitamin K olecule polypeptide and so on. Therefore, natto is known as “super healthy food”.

## 2.2.1. Nattokinase

Nattokinase (EC 3.4.21.62) is a kind of serine protease [10]. Compared with other human thrombolytic agents, including urokinase, tissue-type plasminogen activator (t-PA) and streptokinase, NK has obvious advantages, including fewer gastrointestinal side effects and better stability [11]. NK has a good

The word “natto” originated from Japan, which is fermented by after ordinary steaming or high-pressure *Bacillus subtilis* natto steaming. It has a special flavor and contains many functional -polyglutamic acid,  $\gamma$ -components, such as nattokinase (NK), superoxide dismutase (SOD), glutathione peroxidase, soy isoflavones, saponins, angiotensin-converting enzyme inhibitors (ACEI), vitamin and small molecule peptides, and so on. All of these components  $\gamma$ -K give natto multiple functions, including improving gastrointestinal health, dissolving blood clots, reducing blood fat [1] [2], lowering blood pressure [3], antioxidation [4], preventing stroke [5], preventing Alzheimer disease [6], preventing atherosclerosis [7], preventing calcium loss [8]. It is of great benefit to human health. Therefore, natto is known as “super healthy food”. With the growing elderly population, it is very important to prevent cardiovascular and cerebrovascular diseases, which are the first killer in the world, and then improve senior citizens’ healthy level and enhance the happiness index. Japan is the longest-lived country in the world, with an average age of 84, according to WHO statistics in 2019. Natto has become a must-have for dining table. There is a popular phrase among Japanese people, which is “Eat natto every meal, live up to 99”. But in our country, although natto industry has been developed for more than 20 years, natto has not been accepted by people for many reasons, one of which is the lack of good propaganda and promotion. The purpose of this paper is to make people realize the importance of natto, and accept natto consciously, eat natto frequently, and finally achieve the purpose of “everyone eats natto, healthy without trouble”. Putting the healthy body and the spiritual civilization as the ultimate goal, we will push forward to create a healthy, sustainable, stable and harmonious society.

## 2. The Development History and Function of Natto

## 2.1. The Development History of Natto

Natto is made of fermented soybean by natto bacteria and similar to our traditional fermented soya beans. Fresh natto is golden in color and soft in taste. If it is picked up with chopsticks, it will have a long thread like mucus. If combined with appropriate condiments, it has a favorite flavor, deeply liked by the Japanese people and regarded as an essential flavor food. Natto has a history of 2000 years so far. There are different opinions on the origin of natto, but most people think that natto originated in China and was brought into Japan during the Tang Dynasty when the eminent monk Jianzhen traveled to Japan to preach. After that, there was a new change of natto in Japan. At first, it was fermented by the natural on the straw and made in the kitchen of the *subtilis Bacillus* bacterium

, it will first be absorbed by liver cells to <sub>2</sub>After taking vitamin K promote the coagulation of normal blood. NK dissolves thrombus and promotes blood <sub>2</sub>promotes blood circulation, while vitamin K can reduce the <sub>2</sub>clotting. For fermented foods rich in NK, vitamin K activity of NK. For a product with high activity of NK, the presence may have a negative impact on the efficacy of NK <sub>2</sub>of vitamin K , coagulation is a complex and <sub>2</sub>[16]. But except for vitamin K comprehensive process. It needs the participation of prothrombin activator, fibrinogen activator, coagulation factor, calcium, platelet and many other substances. Any single component can't complete the process of coagulation. Under normal circumstances, vitamin had be <sub>2</sub> would not cause blood clotting even if large amount of K<sub>2</sub>K taken ([http://j-nattokinase.org/jnka\\_nk\\_english.html](http://j-nattokinase.org/jnka_nk_english.html)). However, under special circumstances, natto or nattokinase products should not be used if the body has a bleeding injury, such as gastric ulcer, hemorrhoid or trauma.

constantly moves through the <sub>2</sub>In addition to the above, vitamin K -Carboxyglutamic acid (GLA) <sub>2</sub>bloodstream and activates Matrix Protein (MGP) which is the regulatory factor of inhibiting vascular can prevent calcium deposits in <sub>2</sub>calcification. As a result, vitamin K the blood vessels and so prevent arteriosclerosis from happening, can also prevent cirrhosis from developing into liver <sub>2</sub>Vitamin K can also activate osteocalcin in bone marrow, <sub>2</sub>cancer. Vitamin K promote the generation of bone protein, and then generate bone together with calcium to increase bone density and prevent fracture, further achieving the purpose of treatment and prevention of osteoporosis. In recent years, it has been found that postmenopausal women often have calcification of blood vessels at the same time of osteoporosis. It is believed that there may be a close relationship between them. MGP can inhibit the calcification of blood vessels and is closely related to bone metabolism [8]. In addition to soybean , which provides another <sub>2</sub>isoflavone, natto is also rich in vitamin K strong evidence for reducing or slowing down menopausal symptoms.

### 2.2.5. Biogenic Amines

Biogenic amines are low-molecular-weight organic compounds containing nitrogen, which are produced when food rots or ferments. For example, putrescine, also known as butanedione, is formed by decarboxylation of ornithine under the catalysis of amino acid decarboxylase. Spermidine is widely distributed in organisms, and is -synthesized by putrescine (butylamine) and decarboxylated S adenosylmethionine (dcSAM) under the catalysis of spermidine synthase. Spermidine and dcSAM can be converted into spermine by adding organic compounds containing 3C and 1N under the catalysis of spermine synthase. Because putrescine, cadaverine, spermine and spermidine are very important components for living cells, biogenic amines can promote the physiological function of human body and play a very important role in regulating the synthesis of nucleic acid and protein and the stability of biological membrane. Spermidine is an inducer of autophagy mechanism, through degrading the damaged proteins to protect the cardiovascular system. Spermidine also has an anti-inflammatory effect and prevents stem cell aging [17]. Moderate intake of spermidine in diet can reduce blood pressure, prevent cardiovascular and cerebrovascular diseases, and reduce the risk of Alzheimer's disease and death [18]. Polyamines are beneficial to prevent aging-related diseases. Fermented natto is a good source of polyamines [19]. However, excessive intake can also cause some adverse reactions. In serious cases, it can also cause cerebral hemorrhage, even endanger our lives. Eating foods rich in tyramine, such as fish or fish products, can cause toxicological reactions, such as headache, migraine, neurological diseases, nausea, vomiting, respiratory diseases and hypertension [20]. Similarly, consumption of histamine-rich foods can cause gastrointestinal, circulatory and respiratory symptoms, flushing, rashes, urticarial and so on [21] [22].

effect on arterial thrombosis mediated by oxidative damage and venous thrombosis induced by inflammation. There are four main aspects of thrombolysis. First, it has a direct hydrolysis effect on cross-linked fiber thrombus, hydrolyzing fibrin into soluble small molecules. Second, NK can stimulate endothelial cells to produce endogenous t-PA, which catalyzes plasminogen into plasmin and then enhances its fibrinolytic activity. Third, NK catalyzes prourokinase into urokinase. Urokinase is not only a kind of thrombolytic agent but also a kind of plasminogen activator (PA). Fourth, NK degrades plasminogen activator inhibitor-1 (PAI-1). PAI-1 is the main factor - by suppressing t-vivoregulating the balance of fibrinolytic system in A to reduce the activation of plasminogen into plasmin. Through degrading PAI-1, NK can regulate the balance among PAI-1, t-PA, plasminogen, plasmin, fibrin protein, and improve the function of thrombolysis [2].

NK just can hydrolyze fibrin, the main substance of thrombus, and can't hydrolyze plasma fibrinogen. So, it doesn't like the traditional thrombolytic drugs which maybe cause the risk of bleeding. This advantage of NK is not possessed by other thrombolytic drugs clinically. In addition, the further clinical study found that NK also had significant inhibition of platelet aggregation and hypertension. Natto mucus contains a substance of lowering blood pressure, the inhibitor of angiotensin converting enzyme (ACE). When people eat it, their blood pressure will be decreased.

### 2.2.2. Soybean Isoflavone

Soybean isoflavone is a kind of non-steroidal and heterocyclic phenolic substance, which is abundant in soybean. Soybean -estradiol) in  $\beta$ isoflavone is similar to mammalian estrogen (17-structure, metabolizes to produce equol in the intestine. So, it is called natural plant estrogen [12]. Soybean isoflavone is also a subclass of flavonoids, which have antioxidant properties. It can sweep away free radicals, the by-product produced by cells in the normal metabolism process, and prevent the occurrence of cancer caused by the damage of free radicals to DNA [13]. Daidzein can enhance catalase activity [4]. Menopause is characterized by decreased estrogen secretion from the ovaries, which contributes to the risk of osteoporosis. Soy isoflavones may act as substitute for natural estrogen to prevent osteoporosis [14]. In conclusion, soybean isoflavones have many benefits for human health, such as preventing menopausal symptoms, breast cancer, prostate cancer, cardiovascular and cerebrovascular diseases, osteoporosis, obesity, diabetes, Alzheimer's disease, virus infection [14].

### -Polyglutamic Acid<sub>2</sub>2.2.3.

The health care function of natto is related to some active substances in mucus. After soybean fermented by natto bacterial, natto mucus is -polyglutamic acid <sub>2</sub>similar to a mixture of fructan, fructose and (PGA), in which PGA is the main component of mucus. PGA is a kind of water-soluble poly amino acid produced by microbial fermentation in nature [15]. Its structure is a polymer with peptide -amino  $\alpha$ -carboxyl and  $\gamma$ bond formed by glutamic acid unit through -group, in which D-glutamic acid is the majority. PGA is a long lasting moisturizer, which can effectively increase the moisturizing function and promote skin health. Its moisturizing effect is 2 - 3 times higher than that of hyaluronic acid. Natto mask products also appeared on the market. PGA also has excellent biocompatibility, biodegradability, non-toxicity and non-pollution, so it can be used as an ideal biomaterial.

### <sub>2</sub>2.2.4. Vitamin K



make garlic natto, sauce natto, fruit natto, milk natto, yogurt natto, etc. Second, we can control the fermentation process to improve the flavor. The fermentation process should not be more than 24 hours, because the time is too long, the activity of natto bacteria will decline, and then a large number of bacteria will die, which will produce a strong ammonia odor. Another way is the fermentation substrate can be changed into small soybean or peeled mung beans to improve the flavor of natto. Meanwhile, the storage time of natto should not be too long, otherwise, the taste will be heavier. Third, through genetic engineering, we can regulate the expression of key genes in the metabolic pathway of odor production to achieve the regulation of flavor. As we mentioned above, PTB gene is considered to be the key gene of BCFAs synthesis. The ammonia odor can be reduced by regulating down the expression of PTB gene [27]. Through the exploration and practice in life, we can effectively improve the flavor of natto and make it become a good healthy product for everyone.

Except for the flavor of natto, we should also pay attention to the standardization of natto, the propaganda and the guidance of national policy in order to deepen the natto industry.

In a word, these functional components of natto could contribute to improving human health as well as increasing the high-quality life especially for the elderly. We hope natto would gain popularity as a health food throughout the world.

## استنتاج

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## Conflicts of Interest

The authors declare no conflicts of interest.

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The US Food and Drug Administration (FDA) recommends that the histamine safety threshold in fish is 500 mg/kg (Food and Drug Administration, 2001). In the process of natto fermentation, the total amount of biogenic amines is 26.47 - 72.97 mg/kg, which can't threaten our body considering the dosage [23]. The content of tyramine with direct toxicity to human body is only between 18.1 - 22.3 mg/kg, which is far lower than the limit standard of 100 - 800 mg/kg according to the limit standard of European Food Safety Authority (EFSA) and FDA. Spermidine is cytotoxic, but the current research results show that the toxic concentration of spermidine is higher than the maximum concentration found in food, so the view that spermidine or spermidine in food is harmful to health hasn't enough proof at present [24] [25]. The research result shows that any kind of substance in food necessary for the body must keep a certain balance. The formation of polyamines is related to soybean materials, [19]. *subtilis Bacillus* but less to

## Bacillus subtilis 2.2.6. Natto

can live and proliferate in the *subtilis Bacillus*. After eating Natto, intestine for several weeks, secrete a variety of enzymes and vitamins to promote the proliferation of intestinal mucosal cells. The cellulose can be coupled with *subtilis Bacillus* materials of natto [15] *Bifidobacterium* oligosaccharides to promote the proliferation of can inhibit spoilage microorganisms that *subtilis Bacillus* [26]. Natto cause abnormal fermentation in the intestine, and prevent diarrhea, dysentery, enteritis and constipation. As a whole, it plays an important role in regulating the microecological balance of intestinal flora. Mucus of natto covering the surface of gastrointestinal mucosa can protect the gastrointestinal system and alleviate drunkenness when drinking alcohol.

## 3. Prospects of Natto

With the trade dispute between China and the United States, the cost of imported soybeans has increased, which has greatly impacted the related domestic industries. This also urges us to change our minds and improve the added value of soybean. Natto is facing such a powerful opportunity. Natto is a kind of functional food with low cost and rich nutrition, which should be developed and promoted vigorously.

However, natto cannot be accepted by most people in our country because of its special smell. There are three sources of flavor. First, ammonia odor is produced when natto bacteria decompose protein during fermentation. Second, the branched chain amino acids (valine, -keto acids under the catalysis of  $\alpha$ leucine and isoleucine) generate -keto  $\alpha$ dehydrogenase, then form aldehydes under the catalysis of acid decarboxylase, and then generate branched-chain short fatty acids (BCFAs) under the catalysis of aldehyde deaminase. BCFAs is an uncomfortable taste in natto [27]. In addition, there is another -keto acid under the  $\alpha$ way, the branched chain amino acids generate catalysis of dehydrogenase, and then form acyl-CoA under the -keto acid deaminase complex, and then generate  $\alpha$ catalysis of BCFAs under the catalysis of phosphotransbutyrylase (PTB). Third, in the process of protein decomposition, some bitter peptides will be produced to make natto bitter. Although bitter peptides have some health care functions, but as a kind of food, bitter peptides are unpopular and unaccepted.

Therefore, we should take various methods to improve the flavor of natto. First, its flavor can be improved by physical methods, making natto into natto ice cream, natto sushi, natto porridge, natto pickled vegetable, to some extent to eliminate some undesirable smell. At present, we have also tried some effective methods, for example, to

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