**Food Research 5 (3) : 446 - 452 (June 2021)**
Journal homepage: http://www.myfoodresearch.com

FOOD RESEARCH

MINI REVIEW

# Natto and miso: an overview on their preparation, bioactive components and health-promoting effects

[1,*]Chan, E.W.C., [2]Wong, S.K., [3]Kezuka, M., [3]Oshiro, N. and [3]Chan, H.T.

[1]*Faculty of Applied Sciences, UCSI University, 56000 Cheras, Kuala Lumpur, Malaysia*
[2]*School of Foundation Studies, Xiamen University Malaysia, Bandar Sunsuria, 43900 Sepang, Selangor, Malaysia*
[3]*Secretariat of International Society for Mangrove Ecosystems (ISME), Faculty of Agriculture, University of the Ryukyus, Okinawa 903-0129, Japan*

***Article history:***
Received: 16 October 2020
Received in revised form: 26 November 2020
Accepted: 5 February 2021
Available Online: 30 May 2021

***Keywords:***
Fermented soy products, Human trials, Isoflavones, Nattokinase, Protection against radiation, Vitamin K2

***DOI:***
https://doi.org/10.26656/fr.2017.5(3).587

## Abstract

Natto and miso are two major traditional fermented soy foods in Japan. Natto is prepared by fermenting cooked soybeans with *Bacillus subtilis* natto. The beans of natto have a sticky outlook, slippery texture, sour aroma and nutty flavour. Bioactive components of natto are nattokinase, bacillopeptidase F, vitamin K2, dipicolinic acid and γ-polyglutamic acid. Miso is a fermented soybean paste widely used to make miso soup. The paste is produced by fermenting cooked soybeans with koji (steamed rice inoculated with *Aspergillus oryzae*). Bioactive compounds of miso include isoflavones and phenolic acids. In this review, the preparation, bioactive components, and health-promoting properties of natto and miso are highlighted. Sources of information referred were from Google Scholar, J-Stage, Science Direct, PubMed, PubMed Central and PubChem.

## 1. Introduction

Soybean [*Glycine max* (L.) Merr.] is one of the most widely cultivated plants in the world that is rich in proteins (40–50%), lipids (20–30%) and carbohydrates (26–30%) (Isanga and Zhang, 2008). Major phenolic compounds present are isoflavones (0.1–5.0 mg/g), comprising genistein, daidzein and glycitein (Figure 1).

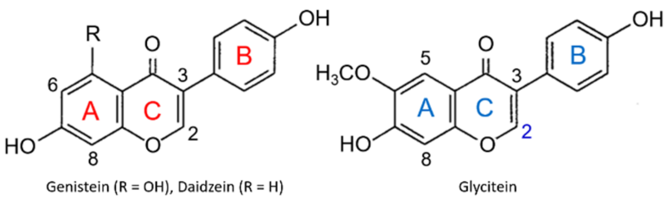


Figure 1. Chemical structures of soy isoflavones

Nutritious, rich in proteins, vitamins and isoflavones, and have health benefits as functional foods, soy foods are very popular in East Asian countries such as Japan, Korea and China (Cao *et al*., 2019). Soy foods are non-fermented (e.g. green soybeans, dry soybeans, soy sprouts and soy milk), or fermented (e.g. soy sauce, tempeh, natto and miso). In Japan, processed soy foods such as soy sauce (shoyu), soybean curd (tofu), soybean paste (miso) and fermented soybeans (natto) are sold in most food stores (Murooka and Yamshita, 2008).

Research has shown that soybean has pharmacological properties such as anti-cancer, anti-diabetic, cardiovascular disease protection, cholesterol reduction, and bone loss prevention properties (Isanga and Zhang, 2008). Recent surveys in Japan showed that a higher intake of natto and miso is associated with a lower risk of mortality (Katagiri *et al*., 2020), and a lower incidence of gestational diabetes (Dong *et al*., 2020).

Katagiri *et al*. (2020) analysed the association between intake of soy products and total and cause-specific mortality in 42,750 men and 50,165 women aged 45–74 years in Japan. Based on the 14.8-year survey, results showed that a higher intake of natto and miso was associated with a significantly lower risk of all-cause mortality. Men and women who consumed natto had a lower risk of cardiovascular mortality than those who did not.

This review begins with an introduction to soybean, non-fermented and fermented soy food products in Japan. Subsequently, emphasis is on natto and miso; their description, preparation, bioactive components and health-promoting effects. The review on natto and miso is unique in that previous reviews are book chapters (Mani and Ming, 2017) or together with other fermented

*Corresponding author.
Email: *chanwc@ucsiuniversity.edu.my, erchan@yahoo.com*

soy products (Murooka and Yamshita, 2008).

## 2. Natto

### *2.1 Description and preparation*

Natto is a fermented soybean product in Japan. Consumed with rice in the morning, natto beans are delicious despite their sticky outlook, slippery texture, sour aroma and nutty flavour. The experience of consuming natto for most foreigners is one of love or hate. The history of natto is thought to have originated from Yunnan province in China (Kuichi, 2001). Another belief is that natto was discovered by accident in the Tohoku region of Japan in the eleventh century when boiled and stored soybeans were accidentally eaten and found to be tasty.

In the preparation of natto, soybeans are first soaked, steamed or boiled, and fermented for 16 hours at 40°C before being allowed to cool and mature for 24 hours in the refrigerator (Kuichi, 2001; Milner and Makise, 2002). The fermentation process is activated by *Bacillus subtilis* natto, a rod-shaped, Gram-positive bacteria with a relatively high heat tolerance of 40–50°C and sourced from rice straw.

### *2.2 Bioactive components*

Natto is a source of novel bioactive components (Cao *et al*., 2019). During fermentation, bioactive components e.g. nattokinase (NK), bacillopeptidase F (BPF), vitamin K2 (menaquinone-7), dipicolinic acid (DPA) and γ-polyglutamic acid (γ-PGA) are generated.

NK is a fibrinolytic protease having 275 amino acid residues and 28 kDa in molecular weight (Fujita *et al*., 1995; Dabbagh *et al*., 2014). The enzyme is heat stable up to 60°C and has a pH range of 6−12 (Milner and Makise, 2002). BPF is a serine protease and has Asp, His and Ser as amino acid sequence (Omura *et al*., 2005). The content of vitamin K2 in natto exceeds 880 mg/100 g (124 times that of soybeans prior to fermentation), making it a very special fermented food item with the highest content of vitamin K2 in the world (Yanagisawa and Sumi, 2005). Equally impressive is the content of DPA in natto, estimated at 21 mg/100 g (Ohsugi *et al*., 2005). γ-PGA, the sticky constituent of natto (Kada *et al*., 2008), resembling spider-web when stirred (Figure 2). It is a polymer in which D- and L-glutamic acids are linked by γ-glutamyl bonds (Ogawa *et al*., 1997). Being water-soluble and biodegradable, γ-PGA has been used to produce biodegradable fibres and hydrogels. Iso-valeric acid and isobutyric acid, are the main volatile compounds responsible for the sour aroma of natto (Kada *et al*., 2008). Prolonged or secondary fermentation of natto releases ammonia.

Figure 2. Natto beans are sticky and stringy

### *2.3 Health-promoting effects*

Natto has attracted attention all over the world as a food that promotes good health and lifespan longevity. Natto also possesses anti-hypertensive (Okamoto *et al*., 1995), inhibition of low-density lipoprotein (LDL) oxidation (Iwai *et al*., 2002), anti-thrombotic (Masada *et al*., 2004), postprandial anti-diabetic (Araki *et al*., 2020), anti-aging (Ibe *et al*., 2013), and reduction in cardiovascular mortality (Nagata *et al*., 2017) activities. Among the bioactive components of natto, NK possesses anti-thrombotic and anti-coagulant activities as shown by animal studies (Fujita *et al*., 1995) and human trials (Kurosawa *et al*., 2015). The anti-thrombotic effect of NK can be used for the treatment of cardiovascular diseases (Weng *et al*., 2017). Anti-hypertensive effects of natto and NK were reported in rats (Ibe *et al*., 2009; Fujita *et al*., 2011). Other bioactivities of NK include amyloid-degradation associated with Alzheimer's disease (Hsu *et al*., 2009), and suppression of atherosclerosis, heart attack and stroke in patients (Ren *et al*., 2017).

The study by Ibe *et al*. (2009) was the first to demonstrate the anti-hypertensive activity of natto *in vivo*. An angiotensin I converting enzyme (ACE) inhibitor produced from natto was orally administered as a single dose (1, 10 and 100 mg/kg body weight) in spontaneously hypertensive (SH) rats, and their blood pressure measured five times every hour. Results showed that administration of the inhibitor, even at the lowest dose, significantly decreased blood pressure after 4 hrs. In another study by Fujita *et al*. (2011), SH rats were fed with NK (0.2 and 2.6 mg/g diet) and its fragments (0.2 and 0.6 mg/g diet). NK and its fragments were absorbed from the intestines and reduced hypertension in rats. NK retained its protease activity and lowered blood pressure through a decrease in blood viscosity by cleaving plasma fibrinogen. Its fragments suppressed hypertension *via* down-regulation of plasma angiotensin II level.

BPF has anti-thrombotic, fibrinolytic and blood

eISSN: 2550-2166

pressure-lowering effects on patients with lifestyle diseases (Hitosugi *et al*., 2015). Vitamin K2 has a dual role in the regulation of bone metabolism i.e. stimulating bone formation and suppressing bone degeneration (Yamaguchi *et al*., 1999). It also prevents bone loss (Ikeda *et al*., 2006) and reduces osteoporotic fracture risk (Kojima *et al*., 2020) among postmenopausal women. DPA has anti-platelet aggregation and anti-blood coagulation activities that are stronger than aspirin (Ohsugi *et al*., 2005). γ-PGA promotes the absorption of calcium in rat intestines (Tanimoto *et al*., 2001).

## 3. Miso

### *3.1 Description and preparation*

Miso including its use and preparation in Japan probably originated from China (Minamiyama and Okada, 2003). It was believed that miso came from jan, a fermented food made from rice or soybean in China. The technique of preparing jan was taught by Ganjin, a Buddhist monk from China, who came to Japan to promote Buddhism.

Miso is a traditional fermented soybean paste used to make miso soup. Three main types of miso sold in the market are white, cream, brown or dark brown in colour (Figure 3). The colour and taste of miso depend on the amount of koji used and salt added, and the duration of fermentation (Kuichi, 2001). Peptides that have undergone the Maillard reaction during fermentation are another important factor (Ogasawara *et al*., 2006). Ripening periods of < 1 month, 3–5 months and 11–15 months yielded miso that are cream, brown and dark brown in colour, respectively. In general, dark brown miso is saltier and stronger in taste. Miso soup is prepared using dashi (bonito stock) as the base.

Figure 3. Light brown miso paste

In the preparation of miso, koji or steamed rice (barley) inoculated with *Aspergillus oryzae* for 40−48 hrs, is used as a starter for the fermentation process (Kuichi, 2001). Soybeans are soaked in water overnight and pressure cooked till they are soft. The beans are then mashed and kneaded with koji, salt and water. The blended paste is then packed into a sealed glass jar and stored in a cool dark place to ferment at 25−30°C. Fermentation can be one week for sweet white miso, 1−3 months for cream-coloured miso and over one year for brown miso.

Besides rice miso (dark brown, brown, cream or white containing different salt content), there are other types such as barley miso, and soy miso (Ohata *et al*., 2009). About 80% of the miso manufactured in Japan is rice miso of which the dark brown miso is most consumed. Miso paste, often made into soup, can also be used as sauce for seasoning or marinade, dressing and dipping.

### *3.2 Bioactive components*

Miso contains substantial amounts of vitamins, minerals, fat, salt, carbohydrates, proteins and microorganisms (Watanabe, 2013). The phenolic constituents include isoflavones (daidzein and genistein) and phenolic acids (vanillic acid and syringic acid) (Minamiyama and Okada, 2003).

### *3.3 Health-promoting effects*

Among the isoflavones and phenolic acids of miso, 8-OH-daidzein, 8-OH-genistein, 6-OH-daidzein and syringic acid had stronger antioxidant activity than α-tocopherol (Hirota *et al*., 2000). 8-OH-genistein and 8-OH-glycitein were strongly cytotoxic towards HL-60 leukaemia cells with $IC_{50}$ values of 9.1 μM and 7.1 μM, respectively (Hirota *et al*., 2004).

The blood pressure of Dahl salt-sensitive (DSS) rats fed with a miso diet (2.3% NaCl) was comparable with those fed with a commercial diet (0.3% NaCl) suggesting that intake of miso did not increase blood pressure in DSS rats (Watanabe *et al*., 2006). Dry dark brown rice miso (Miso Central Institute, Tokyo, Japan) fermented for 180 days was used. In a follow-up study, stroke-prone spontaneously hypertensive (SPSH) rats were given a miso diet (2.8% NaCl), a high salt diet (2.8% NaCl) and a low salt diet (0.3% NaCl) (Watanabe *et al*., 2017). Results showed a significantly higher mortality rate in the high-salt group compared to the miso group and the low-salt group.

Yoshinaga *et al*. (2012) found that long-term consumption of miso soup attenuated blood pressure increase, hypertension and kidney damage in DSS rats, attributable to the possible retardation of sodium absorption in the gastrointestinal tract. The attenuation of salt-induced hypertension in DSS rats was demonstrated by subcutaneous administration of miso (50 mg/day) for 14 days (Shimizu *et al*., 2015). A study reported lower blood pressure in DSS rats after consuming miso soup containing 0.65% saline solution was due to increased diuresis and natriuresis through the dopamine system in

eISSN: 2550-2166 

the kidney (Du *et al*., 2014). Two types of miso administered orally to SPSH rats showed that the ACE inhibitory activity of the specially produced shinki miso was ten-fold stronger than the commercial nenrin miso (Tomari *et al*., 2019). In a recent review on the health benefits of habitual consumption of miso soup, it was concluded that the intake of miso soup does not increase blood pressure and heart rate compared with the equivalent intake of salt, in part due to the lowering of sympathetic nerve activity (Ito, 2020).

The chemopreventive and anti-cancer effects of miso have been reported in rats with mammary cancer (Baggott *et al*., 1990; Gotoh *et al*., 1998) and colon cancer (Ohuchi *et al*., 2005). Human trials also showed that miso can reduce the risk of gastric cancer (Hirayama *et al*., 1981) and liver cancer (Sharp *et al*., 2005). In a national cohort survey, Yamamoto *et al*. (2003) reported that frequent consumption of miso soup and isoflavone reduces the occurrence of breast cancer among women in Japan. A five-year Japan Public Health Centre-based Prospective (JPHCP) Study comparing the impact of fermented and unfermented soy intake on the risk of liver cancer among 75,089 Japanese adults reported no association between total soy intake, fermented and unfermented, and risk of liver cancer (Abe *et al*., 2020). Only for miso intake, there was an inverse association with liver cancer among men.

The earliest and most unique health-promoting effect of miso was its protection against radiation injury (Watanabe *et al*., 2013). On 9 August 1945, when the second atomic bomb devastated Nagasaki in Japan, Tatsuichiro Akizuki (a physician at the St. Francis Hospital) did not suffer from acute radiation, which he attributed to daily consumption of miso soup with wakame seaweed. Dr T. Akizuki is probably the first person to report on the protective properties of miso against radiation. Subsequent, a series of animal studies were conducted on the protective effects of miso against radiation (Watanabe *et al*., 2013). Main findings were that miso with prolonged fermentation was more potent, the mechanisms of protection depended on the compounds produced during fermentation, and the dose of radiation is of paramount importance.

## 4. Conclusion

In Japan, natto and miso are produced locally and on an industrial scale and have one of the longest histories in the food industries. Fermentation methods, standardization of manufacturing procedures, quality controls are well established. The consumption of natto and miso has been associated with health benefits such as lower incidence of certain diseases, and lower risk of mortality. Research and development of natto and miso as functional food need further studies. They include the formulation for specific target groups such as patients with diabetes or hypertension; identification and isolation of bioactive components and understanding their functions and molecular mechanisms; improvement in their taste and efficacy of fermentation methods; standardization of manufacturing procedures; development of criteria for quality control; more human trials in affirming health claims; and monitoring potential toxicity due to excessive dietary intake. Of special interest in their health-promoting effects is further research on the anti-thrombotic, anti-hypertensive, anti-diabetic and anti-aging effects of natto, and on the protection against radiation and anti-cancer effects of miso.

## Conflict of interest

The authors declare no conflict of interest.

## References


Abe, S.K., Sawada, N., Ishihara, J., Takachi, R., Mori, N., Yamaji, T., Shimazu, T., Goto, A., Iwasaki, M., Inoue, M. and Tsugane, S. (2020). Comparison between the impact of fermented and unfermented soy intake on the risk of liver cancer: the JPHC Study. *European Journal of Nutrition*, 60, 1389-1401. https://doi.org/10.1007/s00394-020-02335-9

Araki, R., Fujie, K., Yuine, N., Watabe, Y., Maruo, K., Suzuki, H. and Hashimoto, K. (2020). The possibility of suppression of increased postprandial blood glucose levels by gamma-polyglutamic acid-rich natto in the early phase after eating: A randomized crossover pilot study. *Nutrients*, 12(4), 915. https://doi.org/10.3390/nu12040915

Baggott, J.E., Ha, T., Vaughn, W.H., Juliana, M.M., Hardin, J.M. and Grubbs, C.J. (1990). Effect of miso (Japanese soybean paste) and NaCl on DMBA-induced rat mammary tumours. *Nutrition and Cancer*, 14(2), 103–109. https://doi.org/10.1080/01635589009514083

Cao, Z.H., Green-Johnson, J.M., Buckley, N.D. and Lin, Q.Y. (2019). Bioactivity of soy-based fermented foods: A review. *Biotechnology Advances*, 37(1), 223–238. https://doi.org/10.1016/j.biotechadv.2018.12.001

Dabbagh, F., Negahdaripour, M., Berenjian, A., Behfar, A., Mohammadi, F., Zamani, M., Irajie, C. and Ghasemi, Y. (2014). Nattokinase: Production and application. *Applied Microbiology and Biotechnology*, 98(22), 9199–9206. https://doi.org/10.1007/s00253-014-6135-3

Dong, J.Y., Kimura, T., Ikehara, S., Cui, M., Kawanishi, Y., Kimura, T. and Ueda, K. (2020). Soy consumption and incidence of gestational diabetes mellitus: The Japan Environment and Children's Study. *European Journal of Nutrition*, 60, 897 – 904. https://doi.org/10.1007/s00394-020-02294-1

Du, D.D., Yoshinaga, M., Sonoda, M., Kawakubo, K. and Uehara, Y. (2014). Blood pressure reduction by Japanese traditional miso is associated with increased diuresis and natriuresis through dopamine system in Dahl salt-sensitive rats. *Clinical and Experimental Hypertension*, 36(5), 359–366. https://doi.org/10.3109/10641963.2013.827702

Fujita, M., Hong, K., Ito, Y., Fujii, R., Kariya, K. and Nishimuro, S. (1995). Thrombolytic effect of nattokinase on a chemically induced thrombosis model in rat. *Biological and Pharmaceutical Bulletin*, 18(10), 1387–1391. https://doi.org/10.1248/bpb.18.1387

Fujita, M., Ohnishi, K., Takaoka, S., Ogasawara, K., Fukuyama, R. and Nakamuta, H. (2011). Anti-hypertensive effects of continuous oral administration of nattokinase and its fragments in spontaneously hypertensive rats. *Biological and Pharmaceutical Bulletin*, 34(11), 1696–1701. https://doi.org/10.1248/bpb.34.1696

Gotoh, T., Yamada, K., Yin, H., Ito, A., Kataoka, T. and Dohi, K. (1998). Chemoprevention of N-nitroso-N-methylurea-induced rat mammary carcinogenesis by soy foods or biochanin A. *Japanese Journal of Cancer Research*, 89(2), 137–142. https://doi.org/10.1111/j.1349-7006.1998.tb00541.x

Hirayama, T. (1981). Relationship of soybean paste soup intake to gastric cancer risk. *Nutrition and Cancer*, 3 (4), 223–233. https://doi.org/10.1080/01635588109513726

Hirota, A., Inaba, M., Chen, Y.C., Abe, N., Taki, S., Yano, M. and Kawaii, S. (2004). Isolation of 8-hydroxyglycitein and 6-hydroxydaidzein from soybean miso. *Bioscience, Biotechnology and Biochemistry*, 68(6), 1372–1374. https://doi.org/10.1271/bbb.68.1372

Hirota, A., Taki, S., Kawaii, S., Yano, M. and Abe, N. (2000). 1,1-Diphenyl-2-picrylhydrazyl radical-scavenging compounds from soybean miso and anti-proliferative activity of isoflavones from soybean miso toward the cancer cell lines. *Bioscience, Biotechnology and Biochemistry*, 64(5), 1038–1040. https://doi.org/10.1271/bbb.64.1038

Hitosugi, M., Hamada, K. and Misaka, K. (2015). Effects of *Bacillus subtilis* var. *natto* products on symptoms caused by blood flow disturbance in female patients with lifestyle diseases. *Interna-tional Journal of General Medicine*, 8, 41–46. https://doi.org/10.2147/IJGM.S76588

Hsu, R.L., Lee, K.T., Wang, J.H., Lee, L.Y. and Chen, R.P. (2009). Amyloid degrading ability of nattokinase from *Bacillus subtilis* natto. *Journal of Agricultural and Food Chemistry*, 57(2), 503–508. https://doi.org/10.1021/jf803072r

Ibe, S., Kumada, K., Yoshida, K. and Otobe, K. (2013). Natto (fermented soybean) extract extends the adult lifespan of *Caenorhabditis elegans*. *Bioscience, Biotechnology and Biochemistry*, 77(2), 392–394. https://doi.org/10.1271/bbb.120726

Ibe, S., Yoshida, K., Kumada, K., Tsurushiin, S., Furusho, T. and Otobe, K. (2009). Antihypertensive effects of natto, a traditional Japanese fermented food, in spontaneously hypertensive rats. *Food Science and Technology Research*, 15(2), 199–202. https://doi.org/10.3136/fstr.15.199

Ikeda, Y., Iki, M., Morita, A., Kajita, E., Kagamimori, S., Kagawa, Y. and Yoneshima, H. (2006). Intake of fermented soybeans, natto, is associated with reduced bone loss in post-menopausal women: Japanese population-based osteoporosis (JPOS) study. *Journal of Nutrition*, 136(5), 1323–1328. https://doi.org/10.1093/jn/136.5.1323

Isanga, J. and Zhang, G.N. (2008). Soybean bioactive components and their implications to health — A review. *Food Reviews International*, 24(2), 252–276. https://doi.org/10.1080/87559120801926351

Ito, K. (2020). Review of the health benefits of habitual consumption of miso soup: focus on the effects on sympathetic nerve activity, blood pressure, and heart rate. *Environmental Health and Preventive Medicine*, 25(1), 1–9. https://doi.org/10.1186/s12199-020-00883-4

Iwai, K., Nakaya, N., Kawasaki, Y. and Matsue, H. (2002). Antioxidative functions of natto, a kind of fermented soybeans: Effect on LDL oxidation and lipid metabolism in cholesterol-fed rats. *Journal of Agricultural and Food Chemistry*, 50(12), 3597–3601. https://doi.org/10.1021/jf011718g

Kada, S., Yabusaki, M., Kaga, T., Ashida, H. and Yoshida, K.I. (2008). Identification of two major ammonia-releasing reactions involved in secondary natto fermentation. *Bioscience, Biotechnology and Biochemistry*, 72(7), 1869–1876. https://doi.org/10.1271/bbb.80129

Katagiri, R., Sawada, N., Goto, A., Yamaji, T., Iwasaki, M., Noda, M., Iso, H. and Tsugane, S. (2020). Association of soy and fermented soy product intake with total and cause specific mortality: prospective cohort study. *British Medical Journal,* 2020, 368:m34. https://doi.org/10.1136/bmj.m34

 

Kojima, A., Ikehara, S., Kamiya, K., Kajita, E., Sato, Y., Kouda, K., Tamaki, J., Kagamimori, S. and Iki, M. (2020). Natto intake is inversely associated with osteoporotic fracture risk in post-menopausal Japanese women. *Journal of Nutrition*, 150(3), 599–605. https://doi.org/10.1093/jn/nxz292

Kuichi, K. (2001). Miso and natto. Food Culture. Retrieved from website: https://www.kikkoman.co.jp/kiifc/foodculture/pdf_03/e_007_010.pdf

Kurosawa, Y., Nirengi, S., Homma, T., Esaki, K., Ohta, M., Clark, J.F. and Hamaoka, T. (2015). A single-dose of oral nattokinase potentiates thrombolysis and anti-coagulation profiles. *Scientific Reports*, 5, 11601. https://doi.org/10.1038/srep11601

Mani, V. and Ming, L.C. (2017). Chapter 19 Tempeh and other fermented soybean products rich in isoflavones, 453−474. In Frias, J., Martinez-Villaluenga, C. and Peñas, E. (Eds). Fermented Foods in Health and Disease Prevention. London, UK: Academic Press. https://doi.org/10.1016/B978-0-12-802309-9.00019-4

Masada, M. (2004). Determination of the thrombolytic activity of natto extract. *Food Style*, 8(1), 92–95.

Milner, M. and Makise, K. (2002). Natto and its active ingredient nattokinase: A potent and safe thrombolytic agent. *Alternative and Complementary Therapies*, 8(3), 157–164. https://doi.org/10.1089/107628002760091001

Minamiyama, Y. and Okada, S. (2003). Chapter 11 Miso: Production, properties and benefits to health, 277−286. In Farnworth, E.R. (Ed). Handbook of Fermented Functional Foods. Boca Raton, London, New York: CRC Press. https://doi.org/10.1201/9780203009727.ch11

Murooka, Y. and Yamshita, M. (2008). Traditional healthful fermented products of Japan. *Journal of Industrial Microbiology and Biotechnology*, 35(8), 791–798. https://doi.org/10.1007/s10295-008-0362-5

Nagata, C., Wada, K., Tamura, T., Konishi, K., Goto, Y., Koda, S., Kawachi, T., Tsuji, M. and Nakamura, K. (2017). Dietary soy and natto intake and cardiovascular disease mortality in Japanese adults: The Takayama study. *American Journal of Clinical Nutrition*, 105(2), 426–431. https://doi.org/10.3945/ajcn.116.137281

Ogasawara, M., Yamada, Y. and Egi, M. (2006). Taste enhancer from the long-term ripening of miso (soybean paste). *Food Chemistry*, 99(4), 736–741. https://doi.org/10.1016/j.foodchem.2005.08.051

Ogawa, Y., Yamaguchi, F., Yuasa, K. and Tahara, Y. (1997). Efficient production of γ-polyglutamic acid by *Bacillus subtilis* (natto) in jar fermenters. *Bioscience, Biotechnology and Biochemistry*, 61(10), 1684–1687. https://doi.org/10.1271/bbb.61.1684

Ohata, M., Tominaga, T., Dubourdieu, D., Kubota, K. and Sugawara, E. (2009). Quantification and odor contribution of 2-furanmethanethiol in different types of fermented soybean paste miso. *Journal of Agricultural and Food Chemistry*, 57(6), 2481–2485. https://doi.org/10.1021/jf803258c

Ohsugi, T., Ikeda, S. and Sumi, H. (2005). Anti-platelet aggregation and anti-blood coagulation activities of dipicolinic acid, a sporal component of *Bacillus subtilis* natto. *Food Science and Technology Research*, 11(3), 308–310. https://doi.org/10.3136/fstr.11.308

Ohuchi, Y., Myojin, Y., Shimamoto, F., Kashimoto, N., Kamiya, K. and Watanabe, H. (2005). Decrease in size of azoxymethane induced colon carcinoma in F344 rats by 180-day fermented miso. *Oncology Reports*, 14(6), 1559–1564. https://doi.org/10.3892/or.14.6.1559

Okamoto, A., Hanagata, H., Kawamura, Y. and Yanagida, F. (1995). Anti-hypertensive substances in fermented soybean, natto. *Plant Foods for Human Nutrition*, 47(1), 39–47. https://doi.org/10.1007/BF01088165

Omura, K., Hitosugi, M., Zhu, X., Ikeda, M., Maeda, H. and Tokudome, S. (2005). A newly derived protein from *Bacillus subtilis natto* with both anti-thrombotic and fibrinolytic effects. *Journal of Pharmacological Sciences*, 99(3), 247–251. https://doi.org/10.1254/jphs.FP0050408

Ren, N.N., Chen, H.J., Li, Y., Mcgowan, G.W. and Lin, Y.G. (2017). A clinical study on the effect of nattokinase on carotid artery atherosclerosis and hyperlipidaemia. *Zhonghua Medical Journal*, 97(26), 2038–2042.

Sharp, G.B., Lagarde, F., Mizuno, T., Sauvaget, C., Fukuhara, T., Allen, N., Suzuki, G. and Tokuoka, S. (2005). Relationship of hepatocellular carcinoma to soya food consumption: A cohort-based, case-control study in Japan. *International Journal of Cancer*, 115(2), 290–295. https://doi.org/10.1002/ijc.20897

Shimizu, N., Du, D.D., Sakuyama, H., Ito, Y., Sonoda, M., Kawakubo, K. and Uehara, Y. (2015). Continuous subcutaneous administration of miso extracts attenuates salt-induced hypertension in Dahl salt-sensitive rats. *Food and Nutrition Sciences*, 6(8), 693–702. https://doi.org/10.4236/fns.2015.68072

 

Tanimoto, H., Mori, M., Motoki, M., Torii, K., Kadowaki, M. and Noguchi, T. (2001). Natto mucilage containing poly-γ-glutamic acid increases soluble calcium in the rat small intestine. *Bioscience, Biotechnology and Biochemistry*, 65(3), 516–521. https://doi.org/10.1271/bbb.65.516

Tomari, H.S., Uchikawa, M., Yamazaki, A., Hirabayashi, S., Yamakawa, S., Kitagawa, M., Yamada, M., Itou, S., Yamamoto, T. and Uehara, Y. (2019). Newly manufactured marukome MK-34-1 miso with angiotensin-converting enzyme inhibitory activity and its antihypertensive effects in genetic hypertensive rat models. *Hypertension Research*, 42 (6), 790–800. https://doi.org/10.1038/s41440-018-0197-z

Watanabe, H. (2013). Beneficial biological effects of miso with reference to radiation injury, cancer and hypertension. *Journal of Toxicologic Pathology*, 26 (2), 91–103. https://doi.org/10.1293/tox.26.91

Watanabe, H., Kashimoto, N., Kajimura, J. and Kamiya, K. (2006). A miso (Japanese soybean paste) diet conferred greater protection against hypertension than a sodium chloride diet in Dahl salt-sensitive rats. *Hypertension Research*, 29(9), 731–738. https://doi.org/10.1291/hypres.29.731

Watanabe, H., Sasatani, M., Doi, T., Masaki, T., Satoh, K. and Yoshizumi, M. (2017). Protective effects of Japanese soybean paste (miso) on stroke in stroke-prone spontaneously hypertensive rats (SHRSP). *American Journal of Hypertension*, 31(1), 43–47. https://doi.org/10.1093/ajh/hpx129

Weng, Y., Yao, J., Sparks, S. and Wang, K.Y. (2017). Nattokinase: An oral antithrombotic agent for the prevention of cardiovascular disease. *International Journal of Molecular Sciences*, 18(3), 523. https://doi.org/10.3390/ijms18030523

Yamaguchi, M., Taguchi, H., Gao, Y.H., Igarashi, A. and Tsukamoto, Y. (1999). Effect of vitamin K2 (menaquinone-7) in fermented soybean (natto) on bone loss in ovariectomized rats. *Journal of Bone and Mineral Metabolism*, 17(1), 23–29. https://doi.org/10.1007/s007740050059

Yamamoto, S., Sobue, T., Kobayashi, M., Sasaki, S. and Tsugane, S. (2003). Soy, isoflavones, and breast cancer risk in Japan. *Journal of the National Cancer Institute*, 95(12), 906–913. https://doi.org/10.1093/jnci/95.12.906

Yanagisawa, Y. and Sumi, H. (2005). Natto bacillus contains a large amount of water-soluble vitamin K (menaquinone-7). *Journal of Food Biochemistry*, 29 (3), 267–277. https://doi.org/10.1111/j.1745-4514.2005.00016.x

Yoshinaga, M., Toda, N., Tamura, Y., Terakado, S., Ueno, M., Otsuka, K., Numabe, A., Kawabata, Y. and Uehara, Y. (2012). Japanese traditional miso soup attenuates salt-induced hypertension and its organ damage in Dahl salt-sensitive rats. *Nutrition*, 28(9), 924–931. https://doi.org/10.1016/j.nut.2011.09.010



eISSN: 2550-2166 