

Natto MK-7™ Benefits White Paper

With Related Research References



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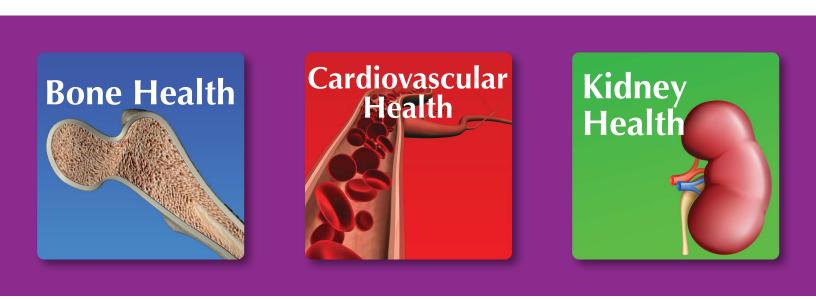
Introduction

<u>Vesta Ingredients</u> Natto MK-7[™] is a dietary supplement that has multiple health benefits. <u>Natto MK-7[™]</u> supports both circulatory and skeletal health. Vesta uses a state-of-theart Supercritical (CO_2) extraction process for manufacturing Natto MK-7[™]. The multiple features of Natto MK-7[™] demonstrates why Vesta Ingredients is a leading supplier of dietary supplements and nutritional ingredients.

Features of Vesta Ingredients Natto MK-7™

- Health support for cardiovascular, skeletal, and renal systems
- New manufacturing process using CO₂ and no solvents
- Environmentally sustainable and clean purification with supercritical extraction
- Concentrated extract with pure MK-7 100% trans-form separation
- Complies with USP 40 Monographs for quality and integrity

Today's consumers do not get enough Vitamin K2 in their diet without proper supplementation. Follow along in this white paper to recognize how Natto MK-7™ Vitamin K2 supplementation can benefit individual health.



Background

Vesta Ingredients provides Natto MK- 7^{TM} as a Vitamin K2 supplement for circulatory and bone health. Natto MK- 7^{TM} is a natural extract of the traditional Asian soy-food "natto." Vesta Ingredients manufactures Vitamin K2 MK-7 (Natto MK- 7^{TM}) with a new, supercritical (CO₂) extraction process. This innovative manufacturing technique and high-quality healthful ingredient is described below.

With CO_2 extractions, there are no solvents or residual components in the MK-7 extracted material. Vesta uses no other extraction solvents, such as hydrocarbon-based propellants like propane and butane, hexane and pentane, or ethanol/alcohol mixtures. Vesta consumers will prefer the manufactured MK-7 product that is made using natural substances, such as CO_2 .

The CO₂ manufacturing process features are summarized below.

- Pure MK-7 "Trans" form, free of cis-isomer impurities
- High-quality Natto MK-7[™] for extensive health support
- Multi-step purification and condensation extraction
- Proprietary manufacturing process as industry leader

Vesta is an established contributor to Vitamin K2 science. In the Spring of 2018, Vesta was recognized by experts as a founding board member of the Vitamin K2 Association. This is documented in recent industry and market news regarding vitamins.

The <u>Vitamin K2 Association</u> has formed with a founding executive board member from Vesta Ingredients (<u>Nutraceuticals World</u>, 30 April 2018)



Structure

MK-7 Vitamin K2 is in a group of several different molecules with side chains of 4 to 14 isoprenoid units. The isoprenoid part of the molecule can be in the cis- or trans-form. Vesta produces only a pure trans-form of Natto MK-7™. MK-7 has a longer half-life and greater potency due to the long-chain, as opposed to the related MK-4. The structure of Vitamin K2 is shown in Figure 1, and the molecular properties of MK-7 Vitamin K2 are below.

Figure 1. Structure of Vitamin K2 MK-7

• CAS No.: 2124-57-4

• Chemical Names: Menaguinone-7; Vitamin K2; Menaguinone K7; Vitamin MK-7

Molecular Formula: C₄₆H₆₄O₂
 Molecular Weight: 649 g/mol

• Appearance: Light yellow microcrystalline powder

Bulk Density: 0.7-0.8 g/ml
Soluble in fats and oils

MK-4 and MK-7

MK-7 is a better form of Vitamin K2 than MK-4. MK-4 is poorly bioavailable at nutritional dose levels but is important in bone building and collagen production. MK-7 allows for the formation of additional MK-4. MK-4 is unstable and has a poor bioavailability, whereas MK-7 is well absorbed and increases the MK-4 levels (Sato et al., 2012). Therefore, MK-7 is a better supplier for MK-4 than MK-4 itself. The MK-7 Vitamin K2 form is better for raising levels of the vitamin in serum than K2 in the MK-4 form (Sato et al., 2012).

MK-7 is from fermented food products whereas MK-4 is from animal meat. Natto MK- 7^{TM} Vitamin K2 is from a non-animal source and is the best form of Vitamin K2. Fermentation is a very efficient and reliable process for natural product preparation with use of highly improved and controlled biological techniques (Demain AL, 2006). Fermentation is the "aging" and transformation of food into healthful substances with healthy bacteria. Natural Vitamin K2 is the byproduct of the fermentation process resulting in Natto MK- 7^{TM} .

Vitamin K2 Deficiency

Vitamin K2 deficiency is extremely common. Many researchers believe that heart disease and osteoporosis are Vitamin K2 deficiencies (Cooking Light Magazine, by Jill Waldbieser, August 30, 2018; accessed September 17, 2018). The role of Vitamin K2 is to get the calcium out of our arteries and into our bones. Adequate K2 helps to reduce both heart and bone issues. Vitamin K2 is not commonly found in foods and is not made in enough

quantities by our bodies. Vitamin K2 supplementation is critical, especially with products like Natto MK-7™.

Health Benefits

MK-7 is also known as Menaquinone-7 and Vitamin K2. Natto MK-7™ is the basis for health from bean consumption in many published scientific studies. A recent study in the European Heart Journal summarizes the circulatory, cardiovascular, and skeletal health benefits of MK-7 supplements (Friberg & Rosenqvist, 2018).

MK-7 works by directing calcium into bones and out of arteries. Although calcium is required to build and maintain bones, excess calcium can deposit in arteries and lead to arterial stiffening. This arterial stiffening or arterial calcification is a leading cofactor in heart disease. Proper MK-7 intake helps to direct calcium towards the bone, and away from arteries.

Bone Health

Vitamin K2 activates a protein called osteocalcin which helps build bones by incorporating calcium into the bone matrix. If Vitamin K2 levels are too low, osteocalcin activation is insufficient and bone formation is reduced. See Figure 2 with high resolution pictures of a femur bone with increasing osteoporosis and bone-loss from left to right.



Figure 2. Femur bone showing increasing osteoporosis and bone-loss from left to right.

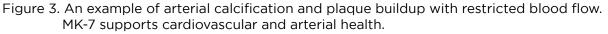
MK-7 supports skeletal health and bones.

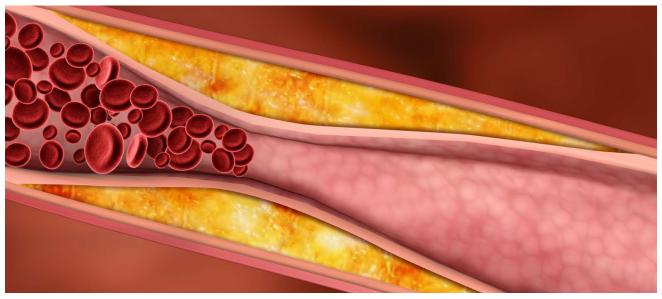
Early studies of MK-7 involved research into coagulation effects and activating proteins like osteocalcin and matrix Gla calcium-regulating protein (MGP). In 1935, Herick Dam named Vitamin K after the coagulation factor, or Koagulation (Dam, 1941). MK-7 regulates calcium with an amino acid that is part of the matrix Gla calcium-regulating protein (MGP). Vitamin K2 activates MGP in cartilage and the smooth muscle cells of the vascular system. The activated MGP binds-up the excess calcium for removal. The lower calcium levels of circulating calcium reduce the risk of calcium deposits in the vessel wall. When untreated, the higher circulating calcium levels result in arterial stiffening which is a risk factor for heart disease. MK-7 helps to minimize arterial stiffness by directing circulating calcium to the bones instead of depositing in the arteries (Knapen et al, 2015).

In another study, MK-7 supplementation was investigated in the age-related decline in bone mineral density and bone strength (Knapen et al, 2013). MK-7 intake significantly decreased age-related decline in bone mineral density. In summary, bone strength was favorably affected by MK-7 supplementation.

Cardiovascular Health

Vitamin K2 is reported to be an important inhibitor of vascular calcification (Barrett et al., 2018; Torii et al., 2016). Higher Vitamin K2 levels are associated with lower coronary artery calcification (CAC; Torii et al., 2016). In addition, Vitamin K2 may have clinical potential to modify the progression of vascular calcification through regulation of functional MGP fractions (Barrett et al., 2018). Figure 3 shows an example of arterial calcification and plaque buildup which restricts blood flow for poor cardiovascular health.





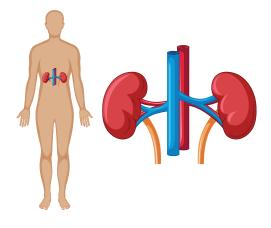
MK-7 supports cardiovascular health by directing calcium into bones and out of arteries. This results in less calcium being deposited in arteries which can lead to arterial stiffening. This arterial stiffening or arterial calcification is a leading cofactor in heart disease. Proper MK-7 intake helps to direct calcium towards the bone, and away from arteries for cardiovascular health support.

Kidney Health

Vitamin K deficiency is common in hemodialysis patients and is significantly correlated with vascular calcifications. The vascular calcifications are also very common among hemodialysis patients. It has been shown that daily doses of menaquinone-7 can be used to support vascular health and improve the health of hemodialysis patients (Aoun et al., 2017). Figure 4 is a diagram of the kidneys and location in the body.

Mansour and team also found MK-7 support for renal function (2017). Renal transplant recipients commonly have an increased risk of cardiovascular disease. It was found that Vitamin K supplementation resulted in an improvement of arterial stiffness and was correlated with cardiovascular support in the renal transplant population (Mansour et al, 2017).

Figure 4. A diagram of the kidneys and location in the body. MK-7 is a Vitamin K2 supplement to support the health of kidney and dialysis patients.



Safety

The safety of MK-7 has been verified. At normal doses, MK-7 displays no toxicity and does not concentrate in the liver unlike other Vitamin K forms (Knapen et al, 2015).

When tested in rodents, MK-7 was determined safe at greater than the limit dose level of 2000 mg/kg body weight for 14 days in mice. In rats, maximum MK-7 dose levels were over 10 mg/kg body weight/day for 90 days with no signs of toxicity (Pucaj et al., 2011). The study concludes that MK-7 is safe for human consumption at typical supplemental doses of Vitamin K.

Proper bone health requires all three of calcium, Vitamin D3, and Vitamin K2. Calcium is needed for building strong bones. MK-7 Vitamin K2 activates the proteins that integrate calcium into bones. Since regular dietary intakes of Vitamin K2 are commonly low, any functional food which supplements with MK-7 can provide a health benefit. In addition,

all products that already contain calcium or Vitamin D3 can benefit from an ingredient enhancement that includes Natto MK- 7^{TM} .

Listed below is a summary of the Natto MK-7™ Health Benefits.

- Natto MK-7[™] helps to regulate calcium levels in bones and arteries
- All-natural produced MK-7 results in high-yield, high-quality, highly-bioavailable, and highly-effective finished product
- Best form of the Vitamin K form for exceptional bioavailability and bioactivity of all Vitamin K vitamers
- Vesta Natto MK-7[™] supports both circulatory and skeletal health

Features of Natto MK-7™

Vesta Ingredients Natto MK-7[™] is unique with many features unlike other competitor products. The features of Natto MK-7[™] are summarized below.

- Purity and optimal bioavailability
- Advanced technology manufacturing
- Health support for BOTH circulatory and skeletal systems
- Common ingredient for leading supplement classes

Optimal Bioavailability with Pure, All-Trans Bioactive MK-7

MK-7 trans form is found in nature and is what is used by the body. Most competitor supplements are a blend of the cis- and trans-form of MK-7. The other impure MK-7 products are a mixture of trans and cis isomers together with other compounds. Competitors sell MK-7 directly after fermentation and the impurities are a common result of the fermentation production process. The Vesta MK-7 is subsequently extracted from the fermentation suspension and purified.

The cis-form of MK-7 competitor products is an impurity with reduced activity and mostly biologically inactive. This MK-7 form is unable to activate K2-dependent enzymes and proteins. Vesta is proud to apply advanced manufacturing technology for the pure, trans form of MK-7, without impurities like competitor products.

Supercritical CO, Manufacturing

Natto MK- 7^{TM} is extracted using a proprietary multi-step process of purification and condensation. This CO_2 extraction is the cleanest, safest method for extracting nutrients from plants such as hops, cannabis and a wide range of organic crops. The supercritical CO_2 extraction methodology delivers a clean, unaltered, and consistent product. Supercritical CO_2 is also a sterilizing process which prolongs shelf life and yields medical-grade nutraceuticals. The relatively low temperature of the process and the stability of CO_2 also allows most compounds to be extracted with little damage or denaturing. See Figure 5 for a representation of the manufacturing process.

New Supercritical Extraction Process for Menaquinone-7 (MK-7)

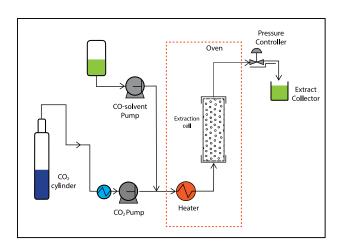


Figure 5. A representation of Vesta's state-of-the-art manufacturing process.

Vesta features Vitamin K2 MK-7 of the best quality and value with the all-natural manufacturing process and pure form. Vesta Ingredients has advanced manufacturing for Natto MK-7TM using the state-of-the-art supercritical (CO_2) extraction process. The CO_2 manufacturing process uses only high pressure and low temperature and no solvents for an all-natural organic product. The Natto MK-7TM is a highly bioavailable and active supplement. The CO_2 results in a concentrated extract with the pure MK-7 100% trans form.

See the numerous research citations which document the benefits of ${\rm CO_2}$ manufacturing at the end of this white paper.

Benefits of Vesta Ingredients MK-7 Supercritical CO_2 Extraction Process:

- \bullet Purity MK-7 with no residual solvent, manufactured with low temperatures and natural ${\rm CO_2}$ to retain ideal organic states, for the cleanest and safest method for extracting plants of nutraceuticals and organic crops
- Efficiency Value-added product manufactured with minimal extraction times, higher yields, low maintenance/energy consumption for cost-efficiency through mechanical innovation
- Sustainable Supercritical extraction with CO₂ as a non-toxic alternative in extraction technology with safer and healthier products for human consumption

Supports BOTH Circulatory and Skeletal Health

The role of Vitamin K2 is to get the calcium out of our arteries and into our bones. Adequate K2 helps to reduce both heart and bone issues. Most diets do not have adequate levels of Vitamin K2 since it is not commonly found in foods and is not made in enough quantities by our bodies. Vitamin K2 supports the health of both the circulatory and skeletal systems. Vitamin K2 supplementation is critical, especially with products like Natto $MK-7^{TM}$.

Leading Supplement Class for Health Benefits

MK-7 provides the same health benefits as other leading dietary supplements including calcium, magnesium, omega-3, and multivitamins. Companies want to participate in providing a supplement in great demand with consumers. Currently, MK-7 is very popular as a supplement like other leading products including calcium, magnesium, omega-3, and multivitamins. Smart businesses will ride the wave of popularity by providing Natto MK-7™ for their customers.

Natto MK- $7^{\text{\tiny M}}$ has unlimited potential. Natto MK- $7^{\text{\tiny M}}$ by Vesta Ingredients can be applied in a variety of formats, and can used in functional foods like energy bars, sports drinks, dietary supplements, and yogurt.

MK-7 Summary

Our diets do not provide us with enough Vitamin K2. Western diets are especially deficient in vitamin K2. Our body cannot produce enough Vitamin K2 and it must be obtained through our diet. Vitamin K2 must be supplemented for optimal bone and heart health. MK-7 is a supplement which provides valuable Vitamin K2 for our bodies. Fermented foods are primary sources of Vitamin K2.

Research indicates that an approximately 100 µg Vitamin K2 daily dose is enough for good bone health. Populations that reach the recommended daily dose of Vitamin K2 were shown to have lower rates of bone and heart disease. These populations include Japanese people who often consume natto which is a dish high in Vitamin K2.

Vitamin K2 deficiency is common in Western populations. A Vitamin K2 deficiency may result in both bone and heart health because of calcium being deposited in arteries instead of bones. Although all people, old and young alike, require Vitamin K2 for optimal

body function, Vitamin K2 deficiencies can be overcome by supplementation.

Vesta Ingredients is proud to introduce Natto MK-7[™] which is manufactured under regulated cGMP guidelines. We are environmentally and socially responsible and dedicated to the nutrition industry. Vesta is committed to be a reliable business partner.

Vesta Ingredients Natto MK-7™ Technology Advantages

- Supercritical (CO₂) extraction process uses only high pressure and low temperature for an environmentally friendly manufacturing process
- No solvents are used resulting in an all-natural organic and wholesome product
- Preserves the original active properties and provides the most bioavailable and bioactive supplement
- Produces a concentrated and pure extract that is very stable and in a highly active ingredient form

Natto MK- $7^{\text{\tiny TM}}$ by Vesta Ingredients provides health support for the circulatory and skeletal system. Our ground-breaking CO_2 manufacturing and extraction process yields a pure, natural, and active form of Vitamin K2. Vesta Ingredients products are used in functional foods like energy bars, sports drinks, dietary supplements, and yogurt. Please call or email Vesta Ingredients for Natto MK- $7^{\text{\tiny TM}}$.

Features of Vesta Ingredients Natto MK-7™

- Health support for Cardiovascular, Skeletal, and Renal systems
- Concentrated extract with pure MK-7 100% trans-form separation
- Highly bioavailable Vitamin K2 from natural source
- Advanced manufacturing process using CO₂ and no solvents
- Environmentally sustainable and clean purification with supercritical extraction
- Complies with USP 40 Monographs for quality and integrity

Publications

More Information

For more information, see the resources below.

nattomk7.com
vitamink2.org
vestanutra.com/vproducts/what-is-nattomk-7
vestaingredients.com

Clinical and Research References:

Aoun M., Makki M, Azar H, Matta H, Chelala DN., BMC Nephrol. 2017; 18-191. <u>High</u> <u>Dephosphorylated-Uncarboxylated MGP in Hemodialysis patients- risk factors and response to vitamin K2.</u>

Barrett, H., O'Keeffe, M., Kavanagh, E., Walsh, M., & O'Connor, E. M. 2018. <u>Is Matrix Gla</u>
Protein Associated with Vascular Calcification? A Systematic Review. Nutrients, 10(4), 415.

Dam H (1941). "The discovery of vitamin K, its biological functions and therapeutical application" (PDF). Nobel Prize Laureate Lecture.

Demain AL. J Ind Microbiol Biotechnol. 2006 Jul;33(7):486-95. <u>From natural products</u> discovery to commercialization: a success story.

Friberg & Rosenqvist, 2018. <u>Less dementia with oral anticoagulation in atrial fibrillation.</u> European Heart Journal, February; 39:6,7.

Knapen MH, Braam LA, Drummen NE, Bekers O, Hoeks AP, and Vermeer C. Thrombosis and Haemostasis. 2015 May;113(5):1135-44. Menaquinone-7 supplementation improves arterial stiffness in healthy postmenopausal women. A double-blind randomised clinical trial.

Knapen MH, Drummen NE, Smit E, Vermeer C, Theuwissen E. Osteoporos Int. 2013 Sep;24(9):2499-507. <u>Three-year low-dose menaquinone-7 supplementation helps</u> decrease bone loss in healthy postmenopausal women.

Mansour AG, Hariri E, Daaboul Y, Korjian S, El Alam A, Protogerou AD, Kilany H, Karam A, Stephan A, Bahous SA. J Am Soc Hypertens. 2017 Sep;11(9):589-597. Vitamin K2 supplementation and arterial stiffness among renal transplant recipients-a single-arm, single-center clinical trial.

Pucaj, K., Rasmussen, H., Moller, M., & Preston, T. 2011, Toxicology Mechanisms and Methods, 21(7), 520–532. <u>Safety and toxicological evaluation of a synthetic vitamin K2, menaguinone-7.</u>

Sato T., Schurgers L.J., and Uenishi K. Nutrition Journal 2012 11:93. <u>Comparison of menaguinone-4 and menaguinone-7 bioavailability in healthy women.</u>

Schwalfenberg K., J Nutr Metab. 2017 Jun 18. <u>Vitamins K1 and K2- The Emerging Group of Vitamins Required for Human Health.</u>

Torii S., Ikari Y., Tanabe K., Kakuta T., Hatori M., Shioi A., Okano T. J. Nutr. Sci. 2016 Dec 29;5:e48. Plasma phylloquinone, menaquinone-4 and menaquinone-7 levels and coronary artery calcification.

MK-7 CO₂ Extraction Process References:

Dorado A D, Hurtado B A, Martínez-Correa HA. Electrophoresis. 2018 Apr 16. <u>Study of supercritical CO₂ extraction of tamarillo (Cyphomandra Betacea) seed oil containing high added value compounds.</u>

Kang SW, Rahman MS, Kim AN, Lee KY, Park CY, Kerr WL, Choi SG. J Food Sci Technol. 2017 Jul;54(8):2485-2493. Comparative study of the quality characteristics of defatted soy flour treated by supercritical carbon dioxide and organic solvent.

Molnar M, Jerković I, Suknović D, Bilić Rajs B, Aladić K, Šubarić D, Jokić S. Molecules. 2017 Feb 24;22(3). pii: E348. Screening of Six Medicinal Plant Extracts Obtained by Two Conventional Methods and Supercritical CO₂ Extraction Targeted on Coumarin Content, 2,2-Diphenyl-1-picrylhydrazyl Radical Scavenging Capacity and Total Phenols Content.

Morales D, Piris AJ, Ruiz-Rodriguez A, Prodanov M, Soler-Rivas C. Biotechnol Prog. 2018 Feb 1. Extraction of bioactive compounds against cardiovascular diseases from Lentinula edodes using a sequential extraction method.

Septavaux J, Germain G, Leclaire J. Acc Chem Res. 2017 Jul 18;50(7):1692-1701. <u>Dynamic</u> Covalent Chemistry of Carbon Dioxide: Opportunities to Address Environmental Issues.

Sookwong P, and Mahatheeranont S. J Oleo Sci. 2017 Jun 1;66(6):557-564. <u>Supercritical CO₂ Extraction of Rice Bran Oil -the Technology, Manufacture, and Applications.</u>

Wrona O, Rafińska K, Możeński C, Buszewski B. J AOAC Int. 2017 Nov 1;100(6):1624 1635. Supercritical Fluid Extraction of Bioactive Compounds from Plant Materials.

<u>Vesta Ingredients</u> is a supplier of dietary supplements and nutritional ingredients. Vesta Nutra supplies nutraceuticals and GMP contract manufacturing Made in the USA. Vesta Ingredients provides supplements for Cognitive, Heart, Bone, and Immune health.

Featured products by <u>Vesta Ingredients</u> include supplements for Cardiovascular, Skeletal, and Cognition health, including <u>Natto NSP-2TM</u> (nattokinase), <u>Natto MK-7TM</u> (Vitamin K2), and <u>Ultra PQQTM</u> (pyrroloquinolone quinone).

See www.vestaingredients.com for information, or email info@vestaingredients.com.





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