

STRONG BONES, with microcrystalline hydroxyapatite, a form of calcium with excellent absorption, is a specific formula for maintaining bone tissue integrity, providing nutrients in adequate amounts to prevent, or effectively reduce, the loss of bone mass. We believe strong bones don't only depend on calcium; other minerals, protein and osteo-specific components are also needed to regulate calcium homeostasis, increase bone density, improve osteoid matrix quality and reduce the risk of fractures from osteoporosis.

**Ingredients:** Calcium salts of orthophosphoric acid (microcrystalline hydroxyapatite), proteins (from microcrystalline hydroxyapatite), L-lysine monohydrochloride, L-proline, glucosamine (from *Aspergillus niger*), magnesium oxide, L-ascorbic acid, magnesium bisglycinate, natural peppermint flavour, anticaking agent: magnesium salts of fatty acids, carrier: citric acid, boric acid, grape seed extract (*Vitis vinifera*), lycopene (from *Lycopersicon esculentum*), green tea leaf extract (*Camellia sinensis*), field horsetail (aerial part) extract (*Equisetum arvense*), zinc monol-L-methionine sulfate, turmeric root extract (*Curcuma longa*), lutein (from *Tagetes erecta*), vitamin D3 (cholecalciferol), manganese citrate, vitamin K2 (menaquinone-4), anticaking agent: silicon dioxide, calcium-L-methylfolate, thiamin hydrochloride, cupric citrate, vitamin B12 (methylcobalamin), vitamin K2 (menaquinone-7), vegetable capsule (glazing agent: hydroxypropylmethylcellulose; purified water).

### Nutritional information:

2 caps. (2.1 g)

|  |                 |
|--|-----------------|
| Calcium (from hydroxyapatite)                          | 300 mg (38%*)   |
| Phosphorus (from hydroxyapatite)                       | 150 mg (21%*)   |
| Proteins (from hydroxyapatite)                         | 300 mg          |
| Magnesium (from Mg bisglycinate)                       | 48.3 mg (**)    |
| Zinc (from Zn mono-L-methionine sulfate)               | 3.1 mg (31%*)   |
| Manganese (from Mn citrate)                            | 0.9 mg (45%*)   |
| Copper (from cupric citrate)                           | 0.31 mg (31%*)  |
| Boron (from boric acid)                                | 1.1 mg          |
| Field horsetail ( <i>E. arvense</i> ) (7% silica)      | 10 mg           |
| Thiamin (vit. B1) (thiamin HCL)                        | 1.4 mg (127%*)  |
| Vit. K2 (menaquinone 4 and 7)                          | 31 µg (41%*)    |
| Vit. D3 (cholecalciferol, 167 IU/caps.)                | 8.3 µg (166%*)  |
| Vit. C (L-ascorbic acid)                               | 62 mg (78%*)    |
| Vit. B12 (methylcobalamin)                             | 50 µg (2 000%*) |
| Folate (calcium-L-methylfolate)                        | 166.7 µg (83%*) |
| L-Lysine   | 100 mg          |
| L-Proline  | 100 mg          |
| Glucosamine sulfate (sodium-free)                      | 84 mg           |
| Turmeric ( <i>C. longa</i> ) (95% curcuminoids***)     | 6.7 mg          |
| Grape seed ( <i>V. vinifera</i> ) (95% PACs)           | 20 mg           |
| Green tea ( <i>C. sinensis</i> ) (5,25mg EGCG/capsule) | 14 mg           |
| Lycopene (from <i>Lycopersicon esculentum</i> )        | 1.7 mg          |
| Lutein (from <i>Tagetes erecta</i> )                   | 0.7 mg          |

\*NRV: Nutrient Reference Value in % \*\*NRV: Nutrient Reference Value below 15%

\*\*\*provides curcumin I, demetoxicurcumin and bisdemetoxicurcumin

### Size and format:

90 and 180 vegetable capsules

### Recommended daily dose:

2 capsules one to three times daily with food. If you are taking medication, take this product a few hours before or after taking them.

Do not exceed the stated recommended daily dose (6 caps.). Do not consume a daily amount of 800 mg of EGCG or more.

### Indications and uses:

The prevention and treatment of any process of decalcification, such as osteoporosis.

### Cautions:

Should not be used by pregnant or lactating women, children below 18 years old, if you are already using other products containing green tea, or on empty stomach. Since fibre can decrease mineral absorption, fibre and minerals should be taken at different times. Patients with a history of renal stones should use precaution when taking calcium supplements due to possible mineral precipitation in the renal pelvis, which can aggravate renal colic. This product should be administered with precaution to patients with gallstones or bile obstruction as well as patients with peptic ulcers or gastric hyperacidity. The effect of certain oral anticoagulant drugs such as Warfarin may be reduced. There may be a certain interaction with anticoagulant and anti-platelet drugs. This product may interfere with glycemic control.

**MICROCRYSTALLINE HYDROXYAPATITE:** Hydroxyapatite is the main mineral component of bone, made up of calcium phosphate crystals and 9 other minerals that intervene in bone formation. It also contains type 1 collagen, a protein that gives resistance and certain flexibility to bone matrix. The inclusion of bovine microcrystalline hydroxyapatite from Australia (BSE free) in our formulation allows us to provide an excellent source of calcium and other minerals (magnesium, chrome, zinc, iron...) in physiological proportions in order to obtain optimal calcium bioavailability, making this calcium more easily absorbed than other calcium supplements<sup>(1,2)</sup>. Different studies suggest that oral administration of hydroxyapatite can accelerate fracture recovery and improve or prevent osteoporosis. Hydroxyapatite represents 99% of body calcium deposits and 80% of total phosphorous, so the main functions of the components found in hydroxyapatite are discussed in detail below<sup>(1,2,3)</sup>:

**CALCIUM:** The importance of this mineral as a constituent of hydroxyapatite crystals has been known for a long time. Calcium concentration in bones isn't only for maintaining bone strength, rather it is the main calcium reservoir for the body. Ageing generates changes in calcium homeostasis. In the elderly, a growing decrease in intestinal calcium absorption has been observed, in association with low vitamin D. Deficient renal tubular calcium resorption has also been described. Menopausal women have been proven to have poor calcium absorption due to hypoestrogenism. We know that people with diets with a low calcium content have a greater risk of fracture. A meta-analysis suggests that for each 300 mg/day of increased calcium intake, hip fracture risk is reduced by 4%. One study proved that for elderly women with previous fractures and low calcium intake, the administration of 1200 mg/day of calcium prevented vertebral fractures. The FDA approves a relationship between calcium supplementation and increased bone mineral density, and said supplementation could reduce the bone fracture rate by 50% as well as improve and prevent osteoporotic pathology<sup>(3)</sup>.

**PHOSPHOROUS:** This micronutrient is another main component of bone. It is found in bone mineral content, forming part of the hydroxyapatite. It's important to maintain an optimal calcium-phosphorous ratio in the diet since phosphorous interferes with the body's calcium balance, and can negatively influence bone metabolism<sup>(4,5)</sup>.

**PROTEIN:** Protein is fundamental for good connective tissue maintenance and provides resistance and traction to extracellular bone matrix. In hydroxyapatite, type 1 collagen is the protein supplying mechanical properties to both bone and tendon<sup>(4,5)</sup>.

**MAGNESIUM:** The body contains 20 to 28 g of magnesium, of which around 60% is found in bone, as part of the bone matrix. This mineral participates in the activity of the parathyroid hormone which regulates bone calcium and vitamin D metabolism. Magnesium supplements are known to increase bone density and reduce fracture risk in menopausal women. In our formula, magnesium has been incorporated in its bisglycinate form to increase its absorption and bioavailability, and is absorbed 4 times faster than other forms of magnesium<sup>(4,6)</sup>.

**L-PROLINE AND L-LYSINE:** The deterioration of bone micro-architecture is directly related to the quality of the osteoid matrix, which is 90% collagen. Any alteration to the collagen in the matrix modifies the bone support needed for mineralization and leads to more fragile, more fracture-prone material. Proline and lysine are two fundamental amino acids for collagen formation. In a study of postmenopausal women with osteoporosis, those who were administered lysine had increased intestinal calcium absorption and better renal conservation of the absorbed calcium. In our formulation, both proline and lysine are present in their free form for better absorption and assimilation<sup>(7)</sup>.

**GLUCOSAMINE SULPHATE WITHOUT SODIUM:** This amino acid participates in the synthesis of glycosaminoglycans and proteoglycans, on behalf of the chondrocytes, which make up joint cartilage. Glucosamine administration favours cartilage restoration and stimulates the synthesis of the above-mentioned compounds in order to maintain bone matrix integrity and improve joint function. Glucosamine sulphate is also attributed an anti-inflammatory action that relieves the symptoms of arthritis<sup>(8)</sup>.

**VITAMIN C (Ascorbic Acid):** Vitamin C intervenes in the maintenance of adequate bone tissue structure. It's necessary for the hydroxylation of proline and lysine in procollagen and to stabilize hydroxyproline in collagen structure. It impedes an excessive extracellular accumulation of pyridinoline, which reduces bone elasticity. It also promotes differentiation of the cells involved in bone development and growth. It's fundamental for osteoclast maturation. Vitamin C is related to both bone density and fracture risk. Several studies have associated high vitamin C intake with increased bone mineral density and have shown that patients with significant vitamin C deficiency are more fracture-prone. Low vitamin C intake increases fracture risk by up to 5 times in smokers, and high serum vitamin C is associated with decreased prevalence of fracture in postmenopausal women who smoke. In another study aimed at determining if vitamin C is related to osteoporotic fractures in non-smoking, older women, those women with osteoporotic fractures were observed to have low serum concentrations of vitamin C<sup>(9)</sup>.

**GRAPE SEED EXTRACT:** Grape seed extract contains proanthocyanidins, which are powerful antioxidants. Diverse experimental studies have clarified the action of proanthocyanidins on bone density. In one study of an arthritis model, the administration of proanthocyanidins in grape seed attenuated the severity of arthritis in a dose-dependent fashion, reducing synovial inflammation

and cartilage and bone erosion. Another study showed that joint administration of calcium and proanthocyanidins was more effective at reversing mandibular bone weakness<sup>(10,11)</sup>.

**GREEN TEA:** Diverse studies have shown a relationship between the polyphenols of green tea, specifically catechins, among which are the EGCG, and bone health. These polyphenols seem to mitigate deterioration and improve bone integrity. They act by suppressing bone erosion and modulating the spongy and endocortical bone compartments, increasing bone mass. The mechanisms of action through which the polyphenols of green tea exert their protective action on bone health have been described in detail in a recent revision<sup>(12)</sup>. These polyphenols would act as potent antioxidants on oxidative stress, as anti-inflammatory agents, strengthening osteoblastogenesis, suppressing osteoclastogenesis and probably exerting some osteoimmunological action<sup>(13,14)</sup>.

**FIELD HORSETAIL:** Because of its high silica content, field horsetail accelerates connective tissue repair, giving it strength and elasticity. In a population study elaborated in order to determine the relationship between silica and bone health, it was concluded that a higher silica intake could have a healthy effect on bone tissue since silica stimulates osteoblast production, neutralizes hydroxyl radicals, participates in the formation of type 1 collagen and promotes structural stability<sup>(15,16)</sup>.

**TURMERIC:** The main compound in turmeric, curcumin, is responsible for its anti-inflammatory effect upon reducing the concentration of cyclooxygenase-2 (COX-2). A high antioxidant action, superior to that of vitamin E, has also been described. Numerous studies relate curcumin with bone microarchitecture. The administration of curcumin in an animal model for 12 months caused changes in bone exchange, preventing deterioration of skeletal structure, and an increase in trabecular bone mass was observed<sup>(17)</sup>.

**ZINC, BORON, MANGANESE AND COPPER (TRACE ELEMENTS):** Among the minerals related to bone health, in addition to those already mentioned (calcium, phosphorous, magnesium, silica), we find zinc, boron, manganese and copper. **ZINC** is necessary for osteoblast activity, collagen synthesis and for the activity of alkaline phosphatase, an enzyme that participates in bone mineralization. Zinc intake through the diet has been proven to influence bone mass peak, reached in adolescence. Supplementation with magnesium, zinc and copper has been associated with a decrease in bone loss during menopause<sup>(18)</sup>. **BORON** is essential for the metabolism of calcium, phosphorous, magnesium and vitamin D<sub>3</sub>. It influences mineral metabolism, improving calcium absorption and reducing its urinary excretion. It also seems to act on collagen turnover, as boron increases collagen synthesis, which can contribute to bone formation<sup>(19)</sup>. **MANGANESE** participates in the synthesis of mucopolysaccharides in the bone matrix. **COPPER** is necessary for collagen structure and for the elastin of said matrix<sup>(4)</sup>.

**LYCOPENE and LUTEIN (CAROTENOIDS):** Different studies have suggested that carotenoids can have a protective effect against the risk of bone mass loss. We have incorporated two carotenoids into our formulation, specifically **LYCOPENE** and **LUTEIN**. LYCOPENE is found mainly in tomato and acts as an antioxidant upon decreasing oxidative stress and the risk of osteoporosis. In a recent study aimed at determining the effects of a lycopene restricted diet on bone turnover markers in postmenopausal women, the researchers concluded that lycopene acts as an antioxidant, decreasing bone destruction. This finding could be beneficial for reducing the risk of osteoporosis. In the Framingham Osteoporosis Study, a correlation was shown between high carotenoid intake, including LUTEIN, and a lower incidence of hip fracture from osteoporosis<sup>(20,21)</sup>.

**VITAMIN B1 (THIAMIN):** Vitamin B<sub>1</sub> intervenes in the enzymatic processes of carbohydrate metabolism for the formation of energy. It's also essential for normal heart and nerve tissue function. This formulation acts in synergy with **vitamin C** and **manganese** for correct bone tissue development. It also improves non-specific muscle pain<sup>(22,24)</sup>.

**FOLATE and VITAMIN B12:** Low levels of folate and vitamin B<sub>12</sub> have been associated with lower bone mineral density and a greater risk of osteoporosis. The existing relationship between these two vitamins and bone health is based on the fact that these two vitamins participate as co-factors in homocysteine metabolism. Homocysteine is involved in osteocalcin synthesis and osteoblast maintenance. It can also interfere with the formation of collagen bridges and the function of diverse proteins in the bone matrix, and perhaps increase osteoclastogenesis. The administration of vitamin B<sub>12</sub> to patients with pernicious anaemia led to an increase in biomarkers of bone formation and improved bone mineral density<sup>(23,25)</sup>.

**VITAMIN K2:** Vitamin K<sub>2</sub> behaves as a co-factor involved in glutamic acid gamma carboxylation, which is an important factor in the production of osteocalcin, a bone-specific protein. There is a relationship between vitamin K intake, bone mineral density and the risk of fracture for the elderly. This is perhaps due to the fact that in the presence of a low vitamin K supply, a less carboxylated and therefore less functional protein is produced. An inverse relationship has been shown between vitamin K intake and hip fracture risk in 72,327 women. We have incorporated vitamin K into our formulation in the forms of menaquinone 4 and 7, which are the most bioavailable forms<sup>(25,27)</sup>.

**VITAMIN D3 (Cholecalciferol):** Vitamin D<sub>3</sub> is the most effective form of vitamin D, regulating the synthesis of other hormones related with calcium metabolism, such as parathormone (PTH), and acts in diverse organs involved in calcium homeostasis, especially in the intestine, favouring intestinal calcium absorption, and is therefore the main regulator of its active absorption. Vitamin D deficiency contributes to increased bone turnover and bone loss. Two out of three women in treatment for osteoporosis present vitamin D deficiency, and among the elderly, 40% present a lack of the vitamin, which rises to 80% among those who live in old people's homes or hospitals<sup>(22,26)</sup>.

#### References:

- 1) Dent, C. E., & Davies, I. J. T. (1980). Calcium metabolism in bone disease: effects of treatment with microcrystalline calcium hydroxyapatite compound and dihydrotachysterol. *Journal of the Royal Society of Medicine*, 73(11), 780-785.
- 2) Ensenat, D., Hassan, S., Reyna, S. V., Schafer, A. I., & Durante, W. (2001). Transforming growth factor-β1 stimulates vascular smooth muscle cell L-proline transport by inducing system A amino acid transporter 2 (SAT2) gene expression. *Biochemical Journal*, 360(2), 507-512.
- 3) Sánchez, A., Puche, R., Zent, S., Oliveri, B., Galich, A. M., Maffei, L., & Bregni, C. (2003). Papel del calcio y de la vitamina D en la salud ósea (Parte II). *Revista Española de Enfermedades Metabólicas Óseas*, 12(1), 14-29.
- 4) Valero et al. (2006). Influencia de la dieta en la salud ósea. *REEMO*. 15(5), 98-104.
- 5) Corbella, M. J. G. (2008). Dieta y fragilidad ósea: estrategia preventiva. *Offarm: farmacia y sociedad*, 27(8), 81-88.
- 6) Sarubin, A. (2000). The Health Professional's Guide to Popular Dietary Supplements. *The American Dietetic Association*. 55-63, 220-225.
- 7) Mendoza, J. M. (2005). Tratamiento farmacológico de la artrosis. Expectativas y realidades. *Revista clinica española*, 205(4), 168-171.
- 8) García, P. H. (2003). ¿Es útil el sulfato de glucosamina en el tratamiento de la artrosis de rodilla? *Semergen: revista española de medicina de familia*, (1), 44-46.
- 9) Martínez-Ramírez, M. J., Palma, S., Delgado-Martínez, A. D., Martínez-González, M. Á., de la Fuente, C., & Delgado-Rodríguez, M. (2007). Vitamina C y riesgo de fractura osteoporótica en mujeres ancianas no fumadoras. Un estudio de casos y controles. *Endocrinología y Nutrición*, 54(8), 408-413.
- 10) Cho, M. L., Heo, Y. J., Park, M. K., Oh, H. J., Park, J. S., Woo, Y. J., & Min, J. K. (2009). Grape seed proanthocyanidin extract (GSPE) attenuates collagen-induced arthritis. *Immunology letters*, 124(2), 102-110.
- 11) Ishikawa, M., Maki, K., Tofani, I., Kimura, K., & Kimura, M. (2005). Grape seed proanthocyanidins extract promotes bone formation in rat's mandibular condyle. *European journal of oral sciences*, 113(1), 47-52.
- 12) Shen, C. L., Yeh, J. K., Cao, J. J., Chyu, M. C., & Wang, J. S. (2011). Green tea and bone health: evidence from laboratory studies. *Pharmacological Research*, 64(2), 155-161.
- 13) Shen, C. L., Yeh, J. K., Samathanam, C., Cao, J. J., Stoecker, B. J., Dagda, R. Y., & Wang, J. S. (2011). Green tea polyphenols attenuate deterioration of bone microarchitecture in female rats with systemic chronic inflammation. *Osteoporosis international*, 22(1), 327-337.
- 14) Shen, C. L., Yeh, J. K., Cao, J. J., & Wang, J. S. (2009). Green tea and bone metabolism. *Nutrition research*, 29(7), 437-456.
- 15) Gierlinger, N., Sapei, L., & Paris, O. (2008). Insights into the chemical composition of Equisetum hyemale by high resolution Raman imaging. *Planta*, 227(5), 969-980.
- 16) Jugdaohsingh, R., Tucker, K. L., Qiao, N., Cupples, L. A., Kiel, D. P., & Powell, J. J. (2004). Dietary silicon intake is positively associated with bone mineral density in men and premenopausal women of the Framingham Offspring cohort. *Journal of Bone and Mineral Research*, 19(2), 297-307.
- 17) Yang, M. W., Wang, T. H., Yan, P. P., Chu, L. W., Yu, J., Gao, Z. D., & Guo, B. L. (2011). Curcumin improves bone microarchitecture and enhances mineral density in APP/PS1 transgenic mice. *Phytomedicine*, 18(2), 205-213.
- 18) Béliveau et al. (2008). Los alimentos contra el cáncer. *Integral*. 115-120.
- 19) Crespo Romero, E. (2001). El boro, elemento nutricional esencial en la funcionalidad ósea.
- 20) Mackinnon, E. S., Venket Rao, A., & Rao, L. G. (2011). Dietary restriction of lycopene for a period of one month resulted in significantly increased biomarkers of oxidative stress and bone resorption in postmenopausal women. *The journal of nutrition, health & aging*, 15(2), 133-138.
- 21) Sahni, S., Hannan, M. T., Blumberg, J., Cupples, L. A., Kiel, D. P., & Tucker, K. L. (2009). Protective effect of total carotenoid and lycopene intake on the risk of hip fracture: a 17-year follow-up from the Framingham Osteoporosis Study. *Journal of Bone and Mineral Research*, 24(6), 1086-1094.
- 22) Grieger, J. A., Nowson, C. A., Jar Vitamins. Salud y equilibrio. man, H. F., Malon, R., & Ackland, L. M. (2009). Multivitamin supplementation improves nutritional status and bone quality in aged care residents. *European journal of clinical nutrition*, 63(4), 558-565.
- 23) Divins MJ. (2004). Vitaminas. Salud y equilibrio. *Farmacia Profesional*. 18(4), 24-30.
- 24) Chover, A. M. (2011). *Medicina ortomolecular*. Editorial Club Universitario. pp.261-66
- 25) Riancho, J. A. (2006). Homocisteína, vitaminas y masa sea. *Revista Española de Enfermedades Metabólicas Óseas*, 15(4), 85-87.
- 26) Tucker, K. L. (2003). Dietary intake and bone status with aging. *Current pharmaceutical design*, 9(32), 2687-2704.
- 27) Kamao, M., Suhara, Y., Tsugawa, N., Uwano, M., Yamaguchi, N., Uenishi, K., & Okano, T. (2007). Vitamin K content of foods and dietary vitamin K intake in Japanese young women. *Journal of nutritional science and vitaminology*, 53(6), 464-470.