

# » OSTEOARTICULAR HEALTH

BONE HEALTH, JOINT HEALTH, INFLAMMATORY PROCESSES



- Exclusive information for health-care professionals-





# **BONE HEALTH**

# **Strong**Bones

### With microcrystalline hydroxyapatite, the most bioavailable form of calcium.

Nutritional information	2 capsules
Minerals:	
Calcium (from hydroxyapatite)	300 mg (38%*)
Phosphorus (from hydroxyapatite)	150 mg (21 %*)
Proteins (from hydroxyapatite)	300 mg
Magnesium (from Mg bisglycinate)	48,3 mg (13%*)
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
Vitamins:	
Thiamin (vit. B1) (thiamin HCL)	1,4 mg (127%*)
Vit. K2 (menaguinone 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%*)
Amino acids:	
Lusine	100 mg
L-Proline	100 mg
Glucosamine (from Aspergillus niger)	84 mg
Antioxidants:	0
Turmeric (Clonga) (95% curcuminoids**)	67 mg
Grape seed (V vinifera) (95% Culcul Initial States)	20 mg
Green tea (C sinensis) (5.25mg ECCC/cans)	14 mg
Lutein (from Tagetes erecta)	0.7 mg
Lycopene (from Lycopersicon esculentum)	1 7 mg
*NRV: Nutrient Reference Value in %	1,7 1118

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

Recommended daily dose: 2 capsules one to three times daily with food.

#### MICROCRYSTALLINE HYDROXYAPATITE\* (MCH) (1-2):

Natural compound main component of the bone matrix.

Organic source of calcium for maximum absorption. It is the most bioavailable form of calcium.

Same type of calcium as found in the bones.

Optimum Calcium-Phosphorus ratio (2:1).

Rich in osteospecific organic components (phosphorus, collagen and proteins) that contribute to stimulate osteogenesis and bone formation.

Source of proteins (type I collagen) essential for the proper maintenance of connective tissue. They afford strength and traction to the bone extracellular matrix.



\*Our MCH is sourced from New Zealand cattle. Certified free of antibiotics, herbicides, pesticides, bovine spongiform encephalopathy (BSE) and recombinant bovine growth hormone (rBGH). Freeze-dried for high quality.

**Strong**Bones

oots



# StrongBones Vegetarian

# New generation vegetarian formula for optimal bone regeneration



Nutritional information:	3 capsules
Minerals:	
Calcium (from calcium phosphate, tribasic)	333 mg (42%*)
Phosphorus (from calcium phosphate, tribasic)	157,4 mg (22%*)
Magnesium (from magnesium bisglycinate)	90 mg (24%*)
Zinc (from zinc mono-L-methionine sulphate)	3,1 mg (31%*)
Manganese (from manganese citrate)	0,9 mg (47%*)
Copper (from cupric citrate)	0,31 mg (31%*)
Boron (from boric acid)	1,1 mg
Field horsetail (Equisetum arvense) (7% silica)	10 mg
Vitaminas:	
Thiamin (vit. B1) (from thiamin hydrochloride)	1,4 mg (127%*)
Vitamin K2 (from menaquinone-4 and menaquinone-7)	31 µg (41%*)
Vitamin D3 (cholecalciferol) (111 IU/caps.)	8,3 µg (166%*)
Vitamin C (L-ascorbic acid)	62 mg (78%*)
Vitamin B12 (methylcobalamin)	50 µg (2.000%*)
Folate (calcium-L-methylfolate)	166,7 µg (83%*)
Amino acids:	
L-Lysine	100 mg
L-Proline	100 mg
Glucosamine (from Aspergillus niger)	84 mg
Antioxidants:	
Turmeric ( <i>Curcuma longa</i> ) (95% curcuminoids**)	7,5 mg
Grape seed (Vitis vinifera) (80% OPC)	20 mg
Green tea ( <i>Camellia sinensis</i> ) (75% EGCG; 3,5 mg/caps.)	14 mg
Lutein (from Tagetes erecta)	0,7 mg
Lycopene (from Lycopersicon esculentum)	1,7 mg
*NRV: Nutrient Reference Value in %.	

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

Recommended daily dose: 3 capsules one to two times daily with food.

#### **TRICALCIUM PHOSPHATE:**

Vegetarian form of calcium for maximum absorption. Of mineral origin instead of MCH of bovine origin.

Supplies 1,000 mg of calcium and 472.23 mg of phosphorus per daily dose.

**GLUCOSAMINE** of plant origin (from *Aspergillus niger*). **VITAMIN D3** from lanolin (not suitable for vegans).



Healthy bone

Osteoporotíc bone



## **BONE HEALTH**

# Common ingredients

# STRONG-BONES & STRONG-BONES Vegetarian

WITH COFACTORS FOR MAXIMUM ABSORPTION



COMPLETE, BROAD-SPECTRUM FORMULAS FOR OPTIMAL BONE HEALTH

NATURAL APPROACH TO PREVENT THE ONSET OF OSTEOPOROSIS

# **Co-Factors** <sup>(11-13)</sup>: for nutrient assimilation and bone formation.

#### Zinc:

Essential for collagen formation and protein synthesis. It contributes to the absorption of vitamins A and E.

#### Manganese

Essential for bone growth and cartilage formation

Contributes to the production of synovial fluid in joints.

#### Copper:

Contributes to the formation of bone, connective tissue and collagen. Together with vitamin C and Zn, it favours the formation of elastin.

#### Silica (from horsetail):

Accelerates the repair of connective tissue in terms of strength and elasticity.

#### Essential amino acids:

L-Proline: necessary for the production of collagen and cartilage for healthy joints, ligaments and tendons. L-Lysine: increases calcium absorption.

#### Vitamin B1 (thiamine):

Reinforces circulation, blood formation, carbohydrate metabolism and digestion.

Important antioxidant.

#### Vitamin K2 (menaquinone 4 and 7):

Inhibits the formation of osteoclasts, which are responsible for bone resorption.

#### Vitamin D3 (cholecalciferol):

Necessary for the absorption of calcium and phosphorus.

#### Vitamin C:

An antioxidant that is crucial for collagen formation Necessary for the repair and growth

of connective tissue.

#### Vitamin B12 (methylcobalamin):

Deficiency of this vitamin is a risk factor for altered bone mineral density.

#### Folate:

Contributes to prevent bone fractures.

#### Glucosamine:

A natural component of cartilage.

#### CALCIUM:

Essential for healthy bones and teeth. Increases growth and bone density. Inhibits bone absorption of toxic metals such as lead.

#### **PHOSPHORUS:**

Essential for the development of bones and teeth, as well as for cell growth.

#### MAGNESIUM BISGLYCINATE (5):

Plays a critical role in calcium absorption. Essential for the metabolism of calcium - vitamin D3.

Magnesium bisglycinate is four times more bioavailable.

**ANTIOXIDANTS** (6-10): Protection against oxidative stress, regulation of inflammatory processes, and the playing of a very important role in bone formation.

#### Turmeric (95% curcuminoids):

Antiinflammatory action.

Related to bone microarchitecture.

#### Grape seed (95% proanthocyanidins):

Improves bone density. Reduces synovial inflammation.

#### Lutein:

Reduces the incidence of hip fracture due to osteoporosis

#### Green tea (75% EGCG):

Improves bone mineral density by enhancing osteoblast formation and suppressing osteoclastogenesis.

#### Lycopene:

Protects osteoblasts from oxidative stress.



#### References:

- Castelo-Branco, C., and J. Dávila Guardia. "Use of ossein–hydroxyapatite complex in the prevention of bone loss: a review." Climacteric 18.1 (2015): 29-37.
- Pines, A., et al. "Clinical trial of microcrystalline hydroxyapatite compound ('Ossopan') in the prevention of osteoporosis due to corticosteroid therapy." Current medical research and opinion 8.10 (1984): 734-742.
- Rüegsegger, P., A. Keller, and M. A. Dambacher. "Comparison of the treatment effects of ossein-hydroxyapatite compound and calcium carbonate in osteoporotic females." Osteoporosis international 5.1 (1995): 30-34.
- Kamhi, Ellen. "Naturopathic Approaches to Preventing and Treating Osteoporosis." Natural Medicine Journal 2.11 (2010).
- Carpenter, Thomas O., et al. "A randomized controlled study of effects of dietary magnesium oxide supplementation on bone mineral content in healthy girls." The Journal of Clinical Endocrinology & Metabolism 91.12 (2006): 4866-4872.
- Rosenthal, Julie M., et al. "Dose-ranging study of lutein supplementation in persons aged 60 years or older." Investigative ophthalmology & visual science 47.12 (2006): 5227-5233.
- Devine, Amanda, et al. "Tea drinking is associated with benefits on bone density in older women." The American journal of clinical nutrition 86.4 (2007): 1243-1247.
- Henrotin, Yves, et al. "Decrease of a specific biomarker of collagen degradation in osteoarthritis, Coll2-1, by treatment with highly bioavailable curcumin during an exploratory clinical trial." BMC complementary and alternative medicine 14.1 (2014): 159.
- Lin, Yumei, et al. "Bone health nutraceuticals alter microarray mRNA gene expression: A randomized, parallel, open-label clinical study." Phytomedicine 23.1 (2016): 18-26.
- Corletto, F. "THERAPEUTICAL NOTES Female climacteric osteoporosis therapy with titrated horsetail (Equisetum arvense) extract plus calcium (osteosil calcium): randomized double blind study," Minerva Ortopedica e Traumatologica 50.5 (1999): 201-206.
- Prentice, Ross L., et al. "Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study." Osteoporosis International 24.2 (2013): 567-580.
- Inaba, Naoko, Toshiro Sato, and Takatoshi Yamashita. "Low-Dose Daily Intake of Vitamin K2 (Menaquinone-7) Improves Osteocalcin -Carboxylation: A Double-Blind, Randomized Controlled Trials." Journal of nutritional science and vitaminology 61.6 (2015): 471-480.
- Whelan, Anne Marie, Tannis M. Jurgens, and Susan K. Bowles. "Natural health products in the prevention and treatment of osteoporosis: systematic review of randomized controlled trials." Annals of Pharmacotherapy 40.5 (2006): 836-849.

# **BONE HEALTH**



# CALCIUM & D<sup>3</sup>.

High potency calcium citrate + vitamin D<sub>3</sub> for maximum absorption.

Nutritional information 1 capsule Calcium citrate 169 mg Vit. D3 (55 IU/caps) 1,4 µg \*NRV: Nutrient Reference Value in %.

Recommended daily dose: 1-4 capsules daily with food.

PREVENTION OF CALCIUM DEFICIENCY STATES

CALCIUM IS THE ESSENTIAL BUILDING BLOCK OF BONES (Osteoporosis)

PREMENSTRUAL SYNDROME AND MENOPAUSE (HELPS TO REDUCE SYMPTOMS)

#### Calcium (citrate) (1-3):

- Contributes to the formation and maintenance of healthy bones and teeth.
- Essential in the contraction mechanism of muscles, including the heart, and in blood clotting.
- Participates in good response of the immune system.

#### Vitamin D<sub>3</sub> (7):

- Stimulates calcium absorption through the small intestine.
- Facilitates the reabsorption of calcium and other minerals in bone.

#### References:

- 1. Spangler, Mikayla, et al. "Calcium supplementation in postmenopausal women to reduce the risk of osteoporotic fractures." American Journal of Health-System Pharmacv 68.4 (2011).
- 2. Reid, I. R., and H. K. Ibbertson. "Calcium supplements in the prevention of steroid-induced osteoporosis." The American journal of clinical nutrition 44.2 (1986): 287-290.
- Napoli, Nicola, et al. "Effects of dietary cal-3. cium compared with calcium supplements on estrogen metabolism and bone mineral

density." The American journal of clinical nutrition 85.5 (2007): 1428-1433.

- Tucker, Katherine L. "Osteoporosis preven-tion and nutrition." Current Osteoporosis 4. Reports 7.4 (2009): 111-117.
- Crespo Romero, Eusebio. "El boro, elemen-5. to nutricional esencial en la funcionalidad ósea." (2001).
- 6. Matarán, Pérez L., et al. "Zinc and osteoporosis." Anales de medicina interna (Madrid, Spain: 1984). Vol. 9. No. 7. 1992.
- 7. Rizzoli, René, et al. "The role of calcium and vitamin D in the management of osteoporosis." Bone 42.2 (2008): 246-249.
- 8. Evia, JR Barva. "Marcadores del Remodelado Óseo y Osteoporosis." Revista Mexicana Patologia Clinica 58.3 (2011): 113-137.
- 9. Badole, Smita, and Swati Kotwal. "Equisetum arvense: Ethanopharmacological and Phytochemical review with reference to osteoporosis." Int J Pharm Sci Health Care 1 (2014): 131-41.
- 10. Kim, Sung-Jin, Hyeon W. Lee, and Ramesh

C. Gupta. "Taurine, bone growth and bone development." Current Nutrition & Food Science 4.2 (2008): 135-144.

- 11. Tanimoto, Hiroyuki, et al. "Acute effect of poly--glutamic acid on calcium absorption in post-menopausal women." Journal of the American College of Nutrition 26.6 (2007): 645-649.
- 12. Clark, Brendon H. "Osteoporosis: The Preventable Epidemic." At: http://consciouslivingcenter.com/wp-content/ uploads/2017/02/Osteoporosis.pdf



# JOINT HEALTH

# JOINT COMPLEX

#### Natural relief of joint pain and inflammation. Strengthens cartilage and connective tissue

A synergistic formula with the supply of an innovative nutrient called **ESM**<sup>®</sup> that affords great support for joint health, improving range of motion and flexibility.

IMPROVES FLEXIBILITY AND ELASTICITY, RELIEVING STIFFNESS OF THE JOINTS

STRENGTHENS CARTILAGE AND CONNECTIVE TISSUE

#### **RELIEVES CONSTRAINTS ON PAINFUL JOINTS**

NATURAL RELIEF OF JOINT PAIN AND INFLAMMATION





Nutritional information:	2 capsules	
ESM® (internal eggshell membrane)	500 mg	
Boswellia serrata (45% boswelllic acid)	260 mg	
Devil's claw ( <i>H. procumbens</i> ) (10% harpagosides)	160 mg	
Turmeric ( <i>C. longa</i> ) (95% curcuminoids*)	200 mg	
Piperine (from black pepper, Piper nigrum)	4 mg	

ESM® is a registered trademark of Torolis S.L

Recommended daily dose: 1 capsule twice daily.

# **BOSWELLIA SERRATA** (35% boswellic acid, 70% organic acids) <sup>(6-7)</sup>

- Boswellic acid possesses antiinflammatory activity, as it inhibits leukotriene production.
- It reduces the degradation of glycosaminoglycans and thus inhibits the degenerative transformation of joint surfaces.
- Boswellic acid together with glucosamine (a component of NEM<sup>®</sup>) exert positive effects by relieving knee pain and stiffness.

#### HARPAGOPHYTUM (5% harpagoside) (8-9)

- It possesses analgesic and antiinflammatory properties due to its harpagoside content.
- It contributes to restore the balance between catabolic and anabolic processes of the extracellular matrix in the joint.

# TURMERIC (95% curcuminoids) AND BLACK PEPPER (piperine) (10-12)

- Antiinflammatory effect; it inhibits the COX-1 and COX-2 enzymes that cause chronic pain and inflammation.
- It inhibits the release of inflammatory mediators (prostaglandin E2, thromboxanes and eicosanoids), affording benefits similar to those of cortisone, but without its toxicity.
- Piperine increases the bioavailability of turmeric by up to 2,000%.

#### References:

- Ruff, Kevin J., et al. "Safety evaluation of a natural eggshell membrane-derived product." Food and chemical toxicology 50.3 (2012): 604-611.
- Benson, Kathleen F., Kevin J. Ruff, and Gitte S. Jensen. "Effects of natural eggshell membrane (NEM) on cytokine production in cultures of peripheral blood mononuclear cells: increased suppression of tumor necrosis factor- levels after in vitro digestion." Journal of medicinal food 15.4 (2012): 360-368.
- Ruff, Kevin J., and Dale P. DeVore. "Reduction of pro-inflammatory cytokines in rats following 7-day oral supplementation with a proprietary eggshell membrane-

derived product." Modern Research in Inflammation 3.01 (2014): 19.

- Ruff, Kevin J., et al. "Eggshell membrane in the treatment of pain and stiffness from osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled clinical study." Clinical rheumatology 28.8 (2009): 907-914.
- Ruff, Kevin J., et al. "Eggshell membrane: a possible new natural therapeutic for joint and connective tissue disorders. Results from two open-label human clinical studies." Clinical interventions in aging 4 (2009): 235.
- 6. Sontakke, S., et al. "Open, randomized,

controlled clinical trial of Boswellia serrata extract as compared to valdecoxib in osteoarthritis of knee." Indian Journal of Pharmacology 39.1 (2007): 27.

- Singh, Surjeet, et al. "Boswellic acids and glucosamine show synergistic effect in preclinical anti-inflammatory study in rats." Bioorganic & medicinal chemistry letters 17.13 (2007): 3706-3711.
- García-García, Pilar, et al. "Propiedades antiinflamatorias de Harpagophytum procumbens: usos tradicionales o evidencia científica?." Revista de Fitoterapia 4.2 (2004): 155-156.
- 9. Crespo Gil, M. Esperanza. "La raíz del

harpagofito en el tratamiento de afecciones reumáticas." Rev. fitoter (2012): 5-14.

- González-Albadalejo, J., et al. "Curcumin and curcuminoids: chemistry, structural studies and biological properties." An Real Acad Farm 81.4 (2015): 278-310.
- Ramsewak, R. S., D. L. DeWitt, and M. G. Nair. "Cytotoxicity, antioxidant and antiinflammatory activities of curcumins I–III from Curcuma longa." Phytomedicine 7.4 (2000): 303-308.
- Shoba, Guido, et al. "Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers." Planta medica 64.04 (1998): 353-356.

# JOINT HEALTH

# (R) Eggshell Membrane

Selection, production and control of raw materials at the source (Navarre, Spain)

Nutraceutical found in the inner membrane of the eggshell.

Powerful natural source of collagen, glucosamine, chondroitin and hyaluronic acid.

They are present in the same proportion as in the joints.



**ESM** is obtained through a natural process by mechanical action, washing and drying that preserves the natural structure of its components.

- SUPPLIES THE HIGHEST AMOUNT OF COLLAGEN ON THE MARKET -



### SCIENTIFIC EVIDENCE

CLINICAL TRIAL IN PATIENTS DIAGNOSED WITH OSTEOARTHRITIS (Universidad Católica de San Antonio de Murcia, 2018)

#### REDUCTION OF PAIN ASSOCIATED WITH THE INFLAMMATORY PROCESS



**IMPROVES FUNCTIONAL CAPACITY BY UP TO 41%** 



#### IT ALSO INCREASES COLLAGEN SYNTHESIS BY SKIN FIBROBLASTS

#### **OTHER STUDIES:**

- Results from another trial involving a dose of 500 » mg showed a 27.8% increase in flexibility after 7 days of treatment and 43.7% at 30 days. Overall pain was reduced by 25.8% at 7 days and 72.5% at 30 days (5).
- Studies have been conducted on the safety » of the inner membrane of the eggshell <sup>(1)</sup>, its antiinflammatory activity (2) and the mechanism of action of such antiinflammatory activity (3).
- » In a clinical trial, it resulted in a 15.9% decrease in pain and a 12.8% reduction of stiffness after only 10 days at a daily dose of 500 mg (4).



### **IMPROVEMENT OF PAIN AND FLEXIBILITY IN JUST 7-10 DAYS**

Composition:	
Protein	94%
Collageno (Types I,V,X)	35%
Elastin	4-5%
Chondroitin sulphate	2%
Hyaluronic acid	2%
Glucosamine	2%
Dermatan and keratan sulphate	1%
Growth factor TGF-β, IGF-1	
Amino acids:	
-Methionine	-Lysine
-Cysteine	-Tryptophan
Other substances:	
-Calcitonin	-Ovocleidin
-Ovocalixin	-Desmosin
-Ovotransferrin	-Isodesmosin

#### **GLYCOSAMINOGLYCANS (GAGS):**

GLUCOSAMINE AND CHONDROITIN: ESSENTIAL POLYSACCHARIDES THAT SERVE AS STRUCTURAL COMPONENTS OF CONNECTIVE TISSUE, INTERSTITIAL FLUIDS AND SKELETAL STRUCTURES.

#### HYALURONIC ACID:

ABUNDANT IN SYNOVIAL FLUID, A LUBRICANT THAT FILLS THE MEMBRANE AND SURROUNDS THE JOINTS.

#### COLLAGEN:

A FIBROUS PROTEIN NECESSARY FOR CARTILAGE STRENGTH AND ELASTICITY.

# Suggestion



# Combine

**Contributes to the growth** and rejuvenation of bone, cartilage, connective tissue and synovial fluid production for a pain-free active lifestyle.

**Contributes to develop** and maintain stronger bones thanks to the adequate form of calcium in Osto-Fort, with cofactors for immediate absorption to prevent osteoarticular problems.

**Relieves joint pain** and stiffness and thus removes the main obstacle to exercise.

**Improves muscle tone**, strengthening and protecting the joints.

STRONG BONES PROVIDE GOOD ATTACHMENT POINTS FOR LIGAMENTS AND TENDONS, ESSENTIAL FOR JOINT STABILITY.

# JOINT HEALTH

# JOINT-TISSU & MSM

#### Complete formula for joint health



CARTILAGE, CONNECTIVE TISSUE AND BONE PROTECTION AND REPAIR

REDUCTION OF INFLAMMATION, SWELLING AND JOINT STIFFNESS

#### AFFORDS JOINT ELASTICITY AND FLEXIBILITY

Nutritional information	1 capsule
Glucosamine sulfate (sodium-free)	300 mg
MSM (methylsulfonylmethane)	300 mg
Shark cartilage	250 mg
Devil's claw (10% harpagosides)	25 mg

Recommended daily dose: 1–2 capsules three times daily with food.

#### **GLUCOSAMINE SULPHATE** (1-2)

- An essential component of native cartilage.
- Essential for the synthesis of glycosaminoglycans (GAGs), proteoglycans and glycolipids, which are responsible for the mechanical and elastic properties of cartilage.

#### METHYLSULFONYLMETHANE (MSM.) (3-4)

- A source of sulphur essential for the formation of chondroitin sulphates.
- It prevents inflammation and facilitates the repair of connective tissue and joints.
- Very effective in musculoskeletal disorders; it shortens the recovery time after sports injuries (joint pain, inflammation, overload, muscle cramps, etc.).

#### SHARK CARTILAGE (5)

- It provides GAGs and other macromolecules found in all our joints.
- These compounds are responsible for maintaining adequate water levels in the cartilage matrix, thus helping to maintain its gel-like nature and protective function.

#### HARPAGOPHYTUM (5% harpagoside) <sup>(6)</sup>

- It possesses analgesic and antiinflammatory properties due to its harpagoside content.
- It contributes to restore the balance between catabolic and anabolic processes of the extracellular matrix in the joint.



The combination of glucosamine and MSM reduces mean pain and swelling in osteoarthritis by 63% and 90%, respectively, after 12 weeks of treatment <sup>(7)</sup>.



#### References

- McAlindon, Timothy E., et al. "Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis." Jama 283.11 (2000): 1469-1475.
- Reginster, Jean Yves, et al. "Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial." The Lancet

357.9252 (2001): 251-256.

- Kim, Yoon Hee, et al. "The anti-inflammatory effects of methylsulfonylmethane on lipopolysaccharide-induced inflammatory responses in murine macrophages." Biological and Pharmaceutical Bulletin 32.4 (2009): 651-656.
- 4. Nakhostin Roohi, Babak, et al. "Effect of chronic supplementation with methylsul-

fonylmethane on oxidative stress following acute exercise in untrained healthy men." Journal of Pharmacy and Pharmacology 63.10 (2011): 1290-1294.

- Sim, Joon-Soo, et al. "Evaluation of chondroitin sulfate in shark cartilage powder as a dietary supplement: Raw materials and finished products." Food Chemistry 101.2 (2007): 532-539.
- Crespo Gil, M. Esperanza. "La raíz del harpagofito en el tratamiento de afecciones reumáticas." Rev. fitoter (2012): 5-14.
- <sup>1</sup> Usha, P. R., and M. U. R. Naidu. "Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis." Clinical drug investigation 24.6 (2004): 353-363.

# **CHONDROITIN & GLUCOSAMINE**

#### Contributes to relieve joint pain associated with osteoarthritis



Protection and care of joint deterioration due to wear and tear, especially in high-impact sports

FACILITATES THE RESTORATION OF FLEXIBILITY, ELASTICITY AND CUSHIONING CAPACITY

Nutritional information	1 capsule
Glucosamine (sodium-free)	500 mg
Chondroitin (90% HPLC)	400 mg

Recommended daily dose: 1-3 capsules daily.

#### **GLUCOSAMINE SULPHATE** (1-2)

- An essential component of native cartilage.
- Essential for the synthesis of glycosaminoglycans (GAGs), proteoglycans and glycolipids, which are responsible for the mechanical and elastic properties of cartilage.

#### CHONDROITIN SULPHATE (3-4)

- Glycosaminoglycan (GAG), which promotes the synthesis of cartilage matrix proteoglycans.
- It exerts antiinflammatory effects, controlling spontaneous pain and improving joint function.
- Without the side effects of nonsteroidal antiinflammatory drugs (NSAIDs) upon the digestive system, kidneys or coagulation.

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# **SCIENTIFIC EVIDENCE**

Comparison of treatment with chondroitin and glucosamine versus celecoxib (NSAID) <sup>(5)</sup>

**Group 1:** 400 mg chondroitin + 500 mg glucosamine, 3 times per day.

**Group 2:** 200 mg celecoxib per day. Study duration: 6 months. Group 2 had more side effects.

	Reduction	Reduction of
	of pain	swelling
Group 1	50,1%	>50%
Group 2	50,2%	>50%



Conclusions: the chondroitin + glucosamine group shows efficacy comparable to *celebiox* in reducing pain, stiffness, functional limitation and swelling/joint effusion after 6 months in patients with knee osteoarthritis. It moreover presents a good safety profile.

#### References:

 Ponce-Vargas, Antonio. "Sulfato de glucosamina. de la condromodulación a la reducción sintomática y del progreso de la artrosis." Seminarios de la Fundación Española de Reumatología 7.1 (2006): 3-11.

2. Reginster, Jean Yves, et al. "Long-term effects of glucosamine sulphate on os-

teoarthritis progression: a randomised, placebo-controlled clinical trial." The Lancet 357.9252 (2001): 251-256.

 Imada, Keisuke, et al. "Anti-arthritic action mechanisms of natural chondroitin sulfate in human articular chondrocytes and synovial fibroblasts." Biological and Pharmaceutical Bulletin 33.3 (2010): 410-414.

 Basallote, S. Giménez, et al. "De la evidencia a la práctica clínica: manejo de la artrosis, II parte." SEMERGEN-Medicina de Familia 34.4 (2008): 193-197.

5. Hochberg, Marc C., et al. "Combined chon-

droitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib." Annals of the rheumatic diseases (2015): annrheumdis-2014.

# M.S.M.

### Provides nutrients for healthy joints



Antiinflammatory and detoxifying action upon the connective tissue Participates in the formation of connective tissue Facilitates recovery from sports injuries Elimination of toxins, allowing the entry of nutrients Strengthens circulation

Nutritional information1 capsuleM.S.M. (methylsulfonylmethane)850 mgRecommended daily dose: 1 or 2 capsules daily with food.

#### METHYLSULFONYLMETHANE (MSM.) (1-3)

- Nutraceutical that plays an important role in the health of skin, hair and nails.
- A source of sulphur, essential for the formation of chondroitin sulphates.
- It prevents inflammation and facilitates the repair of connective tissue and joints.
- Very effective in musculoskeletal disorders; it shortens the recovery time after sports injuries (joint pain, inflammation, overload, muscle cramps, etc.).
- It exerts an analgesic effect due to blocking of the transmission of pain impulses along C nerve fibres.





### **SCIENTIFIC EVIDENCE**

Studies have reported that patients with osteoarthritis who received MSM for 12 weeks showed improvement in pain and physical function <sup>(4-5)</sup>.



#### References:

- Kim, Yoon Hee, et al. "The anti-inflammatory effects of methylsulfonylmethane on lipopolysaccharide-induced inflammatory responses in murine macrophages." Biological and Pharmaceutical Bulletin 32.4 (2009): 651-656.
- 2. Nakhostin Roohi, Babak, et al. "Effect of

chronic supplementation with methylsulfonylmethane on oxidative stress following acute exercise in untrained healthy men." Journal of Pharmacy and Pharmacology 63.10 (2011): 1290-1294.

3. Usha, P. R., and M. U. R. Naidu. "Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis." Clinical drug investigation 24.6 (2004): 353-363.

 Debbi, Eytan M., et al. "Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study." BMC complementary and alternative medicine 11.1 (2011): 50.

 Kim, L. S., et al. "Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial." Osteoarthritis and Cartilage 14.3 (2006): 286-294.

# **AID-INFLAM**

#### Combination of plant extracts (boswellia and turmeric) with bromelain and quercetin



Nutritional information	2 capsules
Boswellia serrata	400 mg
Boswellic acids 35%	140 mg
Organic acids 70%	280 mg
Turmeric (Curcuma longa)	
(95% curcuminoids*)	400 mg
Bromelain	200 mg
(2.400 GDU/g)	7,2 mill. FCC-PU
Quercetin	200 mg

bisdemetoxicurcumin.

Recommended daily dose: 2 cáp. 1-3 veces al día.

Osteoarthritis, rheumatic diseases and sports injuries Reduces inflammation and pain Natural COX-2 inhibitor

#### **BOSWELLIA SERRATA AND TURMERIC** <sup>(1-4)</sup>

- They inhibit the action of cyclooxygenase-2 (COX-2), an enzyme that triggers the production of prostaglandins involved in the inflammation process.
- Boswellia protects cartilage and connective tissue against glycosaminoglycan degradation.
- Turmeric is a potent antioxidant capable of inhibiting the production of free radicals.

#### BROMELAIN (5,6)

- A proteolytic enzyme obtained from pineapple.
  - It degrades pain-related kinins, dissolves fibrin clots and thus reduces inflammation and oedema.
- It regulates type 2 prostaglandins, which are involved in the onset of inflammatory processes.

#### 

- A natural bioflavonoid found especially in onions and apples.
- It blocks COX-2, LOX-5, inhibiting the acute phases of inflammation.
- It also possesses antiallergic properties due to its ability to inhibit histamine production.

# » Mechanism of action of the COX-2 inhibitors



#### References:

- Singh, G. B., and C. K. Atal. "Pharmacology of an extract of salai guggal ex-Boswellia serrata, a new non-steroidal antiinflammatory agent." Agents and actions 18.3-4 (1986): 407-412.
- Siddiqui, M. Z. "Boswellia serrata, a potential antiinflammatory agent: an overview." Indian journal of pharmaceutical

sciences 73.3 (2011): 255-261.

- Mesa, M. D., et al. "Efectos farmacológicos y nutricionales de los extractos de *Curcuma longa* L. y de los cucuminoides." 41.3 (2000): 307-321.
- Murray, Micheal T, N.D., "Curcumin: A Potent Anti Inflammatory Agent", American Journal Of Natural Medicine 1.4 (1994).
- Taussig, Steven J., and Stanley Batkin. "Bromelain, the enzyme complex of pineapple (*Ananas comosus*) and its clinical application. An update." Journal of ethnopharmacology 22.2 (1988): 191-203.
- Fitzhugh, David J., et al. "Bromelain treatment decreases neutrophil migration to sites of inflammation." Clinical

immunology 128.1 (2008): 66-74.

 Valério, Daniel A., et al. "Quercetin reduces inflammatory pain: inhibition of oxidative stress and cytokine production." Journal of Natural Products 72.11 (2009): 1975-1979.

# **INFLA-HEAL PLUS**

#### Inflammation & joints. Complete enzyme, zinc and antioxidant formula



Nutritional information	2 capsules
Pancreatic enzymes 4X	500 mg
Protease	50 000 USP-PC
Amylase	50 000 USP-AGU
Lipase	10 000 USP-LU
Bromelain (2.500 GDU/g)	345,6 mg; 864 GDU
Papain	3 600 000 USP-PU
Trypsin	36 000 USP-TU
Providing:	
Chymotrypsin	720 USP-CU
Rutin	170 mg
L-Cystein (HCl)	20 mg
Zinc	5,2 mg (52%*)
*NRV: Nutrient Reference Valu	ie in %.

Recommended daily dose: 1 capsule two to four times daily between meals.

# MULTI-ENZYME FORMULA A NATURAL WAY TO TREAT ACUTE AND CHRONIC INFLAMMATION. ACCELERATES RECOVERY FROM TISSUE INJURIES RESTORES JOINT MOBILITY AND IMPROVES CIRCULATION

#### ENZYMES (1-4)

- Pancreatin contains protease, which breaks down proteins in damaged tissues, accelerating their recovery.
- Bromelain and papain regulate prostaglandin production and reduce inflammation.
- Trypsin and chymotrypsin are also proteolytic enzymes that reduce inflammation.

#### RUTIN AND L-CYSTEINE (5,6)

- Rutin is a bioflavonoid that possesses antioxidant and antiinflammatory properties.
  - L-cysteine is an amino acid with an antioxidant action that reduced glutathione (GSH) balance. Any imbalance of GSH can contribute to the death of damaged cells.

#### 

- An essential mineral that functions synergistically with the enzyme SOD.
- It is essential for 30 other enzymes, some of which are critical for immune cells to replicate and keep chronic inflammation under control.

# » Antiinflammatory mechanism of action of enzymes

cytokines to the complex.



complex with proteolytic enzyme.

Other antiinflammatory mechanisms of enzymes

- » Degradation of plasma proteins in the interstitial space in acute inflammation, eliminating inflammatory mediators.
- » Blocking of prostaglandin type 2 (PEGE2) synthesis.
- » Modulation of TGF- $\beta$  expression.
- » Anti-oedema and fibrinolytic activity. They increase tissue permeability by promoting oedema reabsorption.
- » They reduce bradykinin, a proinflammatory peptide.

Systemic enzymes (bromelain, papain, trypsin, chymotrypsin) form a complex with the plasma glycoprotein alpha 2-macroglobulin, favouring the elimination of excess cytokines (IL-1, IL-6, IFN- $\gamma$  and TNF- $\beta$ ) and reducing inflammation.

#### References:

- Bucci, Luke R., and J. C. Stiles. "Sports injuries and proteolytic enzymes." Today's Chiropractor 16 (1987): 31.
- Rathnavelu, Vidhya, et al. "Potential role of bromelain in clinical and therapeutic applications." Biomedical reports 5.3 (2016): 283-288.
- 3. Emele, J. F., et al. "The analgesic-antiinflammatory activity of papain." Archives

internationales de pharmacodynamie et de therapie 159.1 (1966): 126-134.

 Kaur, R., et al. "Trypsin, rutoside and bromelain alone and fixed dose combination: a natural, safer and effective antiinflammatory agent." Journal of Drug Delivery and Therapeutics 4.1 (2014): 108-110.

5. Guardia, Teresita, et al. "Anti-inflammatory

properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat." Il farmaco 56.9 (2001): 683-687.

 Song, Ze he, et al. "L-Cysteine protects intestinal integrity, attenuates intestinal inflammation and oxidant stress, and modulates NF-κB and Nrf2 pathways in weaned piglets after LPS challenge." Innate immunity 22.3 (2016): 152-161.

 Dirajlal-Fargo, Sahera, et al. "Brief report: zinc supplementation and inflammation in treated HIV." Jaids Journal of Acquired Immune Deficiency Syndromes 82.3 (2019): 275-280.

# **Collagen MultiMax 5**



#### Collagen (1,2):

• Contributes to maintain the structural integrity of joints, bones and cartilage. Helps repair joint damage, muscle recovery, prevent age-related sarcopenia, etc.

#### ESM® (EGGSHELL INNER MEMBRANE) (inner membrane of the eggshell ) (3,4):

- A natural source of glycosaminoglycans, glucosamine, chondroitin and hyaluronic acid, essential for maintaining healthy cartilage and synovial fluid.
- It possesses antiinflammatory action, reducing joint pain and stiffness.

#### Hyaluronic acid (5,6):

- Present in all connective tissues and organs, such as skin, synovial fluid, etc.
- In patients with osteoarthritis of the knee, it helps to reduce pain, improve physical function and improve quality of life.

#### Vitamin C (7,8):

- Crucial for collagen synthesis, which is essential for the proper functioning of bones, teeth, cartilage, gums, skin and blood vessels.
- It can help accelerate bone healing after fracture and speed recovery from musculoskeletal damage by increasing type I collagen synthesis and reducing oxidative stress parameters.

#### Magnesium (9,10):

- A cofactor in many enzymatic processes needed for cellular energy utilization.
- It is essential for the correct metabolism and absorption of calcium.
- It exerts a positive effect upon stress states and has a calming action. It improves heart activity and regulates fats and glucose in the blood.

#### Copper (11-13):

- Necessary for the collagen and elastin structure of the bone matrix. It is a cofactor of the enzyme lysyl oxidase, which is needed for the formation of lysine-derived cross-links in collagen and elastin.
- It also plays a key role in inhibiting bone resorption, preventing calcium loss from the bones.

#### Silica (14,15):

- Accelerates the repair of connective tissue, affording strength and elasticity.
- Exerts effects on bone tissue because it stimulates the production of osteoblasts, participates in the formation of type I collagen and promotes its structural stability.

#### Boron (16,17):

- Essential for the metabolism of calcium, phosphorus, magnesium and vitamin D3.
- It influences mineral metabolism by improving calcium absorption and reducing urinary excretion.
- Intervenes in collagen turnover, since it increases collagen synthesis, contributing to bone formation.

#### Malic acid (18,19):

- It is the basis of the start of the Krebs cycle, which is crucial for energy production.
- It increases the amount of malate in mitochondria, thereby increasing the energy production capacity of the cell, reducing fatigue and improving exercise tolerance.

#### Harpagophytum (Devil's claw) (20,21):

- Harpagoside possesses analgesic and antiinflammatory properties; its main function is to inhibit the release of cytokines that contribute to the inflammatory process.
- It inhibits the catabolic processes that lead to the degradation of joint cartilage.

# **Collagen MultiMax 5**





Nutritional information	Per serving 11 g	Per 100 g
Energy (kJ/kcal)	136/32	1.240/295
Fats	0,0 g	0,4 g
Saturates	0,0 g	0,0 g
Carbohydrate	1,1 g	9,8 g
Sugars	0,0 g	0,1 g
Fibre	0,0 g	0,3 g
Protein	7 g	63 g
Salt	0,5 g	4,1 g
Other nutrients:	Per serving 11 g	VRN*
Hydrolyzed porcine collagen (type I y III)	5 000 mg	
Hydrolyzed chicken collagen (type II)	40 mg	
Hydrolyzed bovine collagen (type I y III)	2 500 mg	
ESM® internal eggshell membrane (type I	, V and X) 300 mg	
Hyaluronic acid	25 mg	
Vitamin C (Ŀascorbic acid)	40 mg	50%
Magnesium (from magnesium citrate)	187,5 mg	50%
Copper (from cupric gluconate)	0,5 mg	50%
Silica (from bamboo extract)	40 mg	
Boron (from boric acid)	3 mg	
Malic acid	500 mg	
Devil's claw (H. procumbens) (6:1)		
(2,5% harpagosides)	150 mg	
*NRV: Nutrient Reference Value in %.		

Recommended daily dose: 1 measuring spoon (11 g) daily.

### A formula with 5 types of collagen, hyaluronic acid, vitamin C, minerals and Harpagophytum

#### References:

- Lugo, James P., Zainulabedin M. Saiyed, and Nancy E. Lane. "Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study." Nutrition journal 15.1 (2015): 1-15.
- Clark, Kristine L., et al. "24-Week study on the use of collagen hydrolysate as a dietary supplement in athletes with activity-related joint pain." Current medical research and opinion 24.5 (2008): 1485-1496.
- Ruff, Kevin J., et al. "Eggshell membrane in the treatment of pain and stiffness from osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled clinical study." Clinical rheumatology 28.8 (2009): 907-914.
- Ruff, Kevin J., et al. "Eggshell membrane: a possible new natural therapeutic for joint and connective tissue disorders. Results from two open-label human clinical studies." Clinical interventions in aging 4 (2009): 235-240.
- 5. Kalman, Douglas S., et al. "Effect of a natural extract of chicken combs with a high

content of hyaluronic acid (Hyal-Joint®) on pain relief and quality of life in subjects with knee osteoarthritis: a pilot randomized double-blind placebo-controlled trial." Nutrition journal 7.1 (2008): 1-9.

- Guadagna, Simone, et al. "Oral hyaluronan for the treatment of knee osteoarthritis: a systematic review." Progr Nutr 20 (2018): 537-44.
- Murad, S., et al. "Regulation of collagen synthesis by ascorbic acid." Proceedings of the National Academy of Sciences 78.5 (1981): 2879-2882.
- DePhillipo, Nicholas N., et al. "Efficacy of vitamin C supplementation on collagen synthesis and oxidative stress after musculoskeletal injuries: a systematic review." Orthopaedic journal of sports medicine 6.10 (2018): 2325967118804544.
- Laires, Maria José, Cristina Paula Monteiro, and Manuel Bicho. "Role of cellular magnesium in health and human disease." Front Biosci 9 (2004): 262-276.
- 10. Bo, Simona, and Elisabetta Pisu. "Role of dietary magnesium in cardiovascular

disease prevention, insulin sensitivity and diabetes." Current opinion in lipidology 19.1 (2008): 50-56.

- Harris, Edward D., et al. "Copper and the synthesis of elastin and collagen." Ciba Foundation Symposium. Vol. 79. 1980.
- Rucker, Robert B., et al. "Copper, lysyl oxidase, and extracellular matrix protein cross-linking." The American journal of clinical nutrition 67.5 (1998): 996S-1002S.
- Wilson, T., J. M. Katz, and D\_H Gray. "Inhibition of active bone resorption by copper." Calcified tissue international 33.1 (1981): 35-39.
- 14. Jugdaohsingh, Ravin. "Silicon and bone health." The journal of nutrition, health & aging 11.2 (2007): 99.
- Jugdaohsingh, R., et al. "Silicon intake is a major dietary determinant of bone mineral density in men and pre-menopausal women of the Framingham Offspring Cohort." Bone. Vol. 32. No. 5. 360 PARK AVE SOUTH, NEW YORK, NY 10010-1710 USA: ELSEVIER SCIENCE INC, 2003.
- 16. Crespo, E. "El boro, elemento nutricional

esencial en la funcionalidad ósea." Rev Esp-CirOsteoart 206 (2001): 88-95.

- Askar, Tünay Kontas, E. R. Hilal, and Ruken Esra Demirdögen. "The Effects of Boron on Bone Metabolism as a Nutraceutical: A Review." Avrasya Saglık Bilimleri Dergisi 1.1 (2018): 7-12.
- Werbach, Melvyn R. "Nutritional strategies for treating chronic fatigue syndrome." Alternative Medicine Review 5.2 (2000): 93-108.
- Sahley, Billie Jay, Katherine M. Birkner, and Katherine M. Birkner. Malic Acid and Magnesium for Fibromyalgia and Chronic Pain Syndrome. Pain & Stress Publications, 1999.
- Álamo, C., et al. "Propiedades antiinflamatorias de Harpagophytum procumbens: sos tradicionales o evidencia científica?." Revista de fitoterapia 4.2 (2004): 155-156.
- Gil, M<sup>a</sup> Esperanza Crespo, and María Concepción Navarro Moll. "La raíz de harpagofito en el tratamiento de las afecciones reumáticas." Revista de fitoterapia 12.1 (2012): 5-20.

# **ANALGESIA AND INFLAMMATION**

# PEA (palmitoylethanolamide)

#### Affords relief from chronic pain and inflammation



#### PALMITOYLETHANOLAMIDE (PEA) (1-21)

- Palmitoylethanolamide is a natural compound produced by the body to protect cells from inflammation and pain.
- It inhibits the release of inflammatory cytokines such as interleukins IL-1 $\beta$  and IL-6, as well as tumour necrosis factor alpha (TNF- $\alpha$ ).
- Clinical trials suggest that PEA may be useful in patients with sciatica, chemotherapy-induced neuropathy, generalized pain, migraine, glaucoma, burning mouth syndrome, major depressive disorder (MDD), autism, myasthenia gravis, carpal tunnel syndrome, temporomandibular joint (TMJ) pain and osteoarthritis of the knee.

#### References:

- Rankin, Linda, and Christopher J. Fowler. "The basal pharmacology of palmitoylethanolamide." International Journal of Molecular Sciences 21.21 (2020): 7942.
- Clayton, Paul, et al. "Palmitoylethanolamide: a natural compound for health management." International Journal of Molecular Sciences 22.10 (2021): 5305.
- Gabrielsson, Linda, Sofia Mattsson, and Christopher J. Fowler. "Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy." British journal of clinical pharmacology 82.4 (2016): 932-942.
- Petrosino, Stefania, and Vincenzo Di Marzo. "The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations." British Journal of Pharmacology 174.11 (2017): 1349-1365.
- Petrosino, Stefania, et al. "The anti inflammatory mediator palmitoylethanolamide enhances the levels of 2 arachidonoyl glycerol and potentiates its actions at TRPV1 cation channels." British Journal of Pharmacology 173.7 (2016): 1154-1162.
- Cruccu, Giorgio, et al. "Micronized palmitoylethanolamide: a post hoc analysis of a controlled study in patients with low back pain-sciatica." CNS & Neurological Disorders-Drug Targets (Formerly Current Drug

Targets-CNS & Neurological Disorders) 18.6 (2019): 491-495.

- Gatti, Antonio, et al. "Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis." Pain Medicine 13.9 (2012): 1121-1130.
- Truini, A., et al. "Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy." CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders) 10.8 (2011): 916-920.
- Papetti, Laura, et al. "Tolerability of palmitoylethanolamide in a pediatric population suffering from migraine: a pilot study." Pain Research and Management 2020 (2020): 3938640.
- Rossi, Gemma Caterina Maria, et al. "Effect of palmitoylethanolamide on inner retinal function in glaucoma: A randomized, single blind, crossover, clinical trial by pattern-electroretinogram." Scientific Reports 10.1 (2020): 1-14.
- Costagliola, Ciro, et al. "Effect of palmitoylethanolamide on visual field damage progression in normal tension glaucoma patients: results of an open-label six-month follow-up." Journal of Medicinal Food 17.9 (2014): 949-954.

- Ottaviani, Giulia, et al. "Efficacy of ultramicronized palmitoylethanolamide in burning mouth syndrome-affected patients: a preliminary randomized double-blind controlled trial." Clinical Oral Investigations 23.6 (2019): 2743-2750.
- Ghazizadeh-Hashemi, Maryam, et al. "Palmitoylethanolamide as adjunctive therapy in major depressive disorder: A double-blind, randomized and placebo-controlled trial." Journal of affective disorders 232 (2018): 127-133.
- Khalaj, Mona, et al. "Palmitoylethanolamide as adjunctive therapy for autism: Efficacy and safety results from a randomized controlled trial." Journal of psychiatric research 103 (2018): 104-111.
- Onesti, Emanuela, et al. "Short-term ultramicronized palmitoylethanolamide therapy in patients with myasthenia gravis: a pilot study to possible future implications of treatment." CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders) 18.3 (2019): 232-238.
- Conigliaro, R., et al. "Use of palmitoylethanolamide in the entrapment neuropathy of the median in the wrist." Minerva medica 102.2 (2011): 141-147.
- 17. Evangelista, Maurizio, et al. "Ultra-micronized palmitoylethanolamide effects on

sleep-wake rhythm and neuropathic pain phenotypes in patients with carpal tunnel syndrome: an open-label, randomized controlled study." CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders) 17.4 (2018): 291-298.

- Marini, Ida, et al. "Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain." Journal of orofacial pain 26.2 (2012): 99.
- Steels, Elizabeth, et al. "A double-blind randomized placebo-controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis." Inflammopharmacology 27.3 (2019): 475-485.
- Brotini, Stefania, Carlo Schievano, and Leonello Guidi. "Ultra-micronized palmitoylethanolamide: an efficacious adjuvant therapy for Parkinson's disease." CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders) 16.6 (2017): 705-713.
- Keppel Hesselink, J. M., Tineke de Boer, and Renger F. Witkamp. "Palmitoylethanolamide: a natural body-own anti-inflammatory agent, effective and safe against influenza and common cold." International journal of inflammation 2013 (2013).

