

# SYNOVX<sup>®</sup> AI

Joint Comfort Support\*



Available in 60 vegetarian capsules

## DISCUSSION

### Type II Collagen

Type II collagen (CII) is the most abundant structural protein in cartilage. It provides tensile strength and toughness to the tissue. In some individuals, immune responses to endogenous CII may impact joint cartilage integrity and joint comfort. However, researchers have discovered that a repetitive low dose of chicken or bovine CII—when taken orally and in its native form—is able to support a naturally balanced and healthy joint environment in such individuals.<sup>[1-3]</sup> This is accomplished through a natural mechanism called oral tolerization (or “oral tolerance”), which supports the body’s desensitization process to a specific antigen—in this case, CII.<sup>[3]</sup> Oral tolerization using CII essentially works as follows:

- Orally administered native CII enters the Peyer’s patches (immune surveillance structures) in the gut-associated lymphoid tissue (GALT).\*
- Dendritic cells in the GALT take up the CII and present it to T-cells to produce regulatory T-cells.\*
- Regulatory T-cells change specific systemic immune responses via the production of certain regulatory cytokines (e.g., TGF-beta 1, IL-10 and IL-4).\*
- Systemic immune tolerance to CII is induced by the body and endogenous CII is naturally protected.\*

Human trials have been conducted to study the effects of oral CII in joint health.<sup>[4-8]</sup> In a multicenter, double-blind, placebo-controlled trial, 205 individuals were enrolled at six different sites and randomized to receive a placebo or an oral dose (20, 100, 500, or 2,500 mcg) of CII for 24 weeks. Efficacy was assessed monthly, and responses were analyzed utilizing three sets of criteria. Positive effects were observed at the lowest dose of CII, and no side effects were detected.<sup>[6]</sup> Trentham et al found beneficial effects on the size and comfort of joints in a randomized, double-blind, placebo-controlled trial involving 60 patients who were given 100-500 mcg/d of chicken CII for three months.<sup>[2]</sup> Ausar et al found beneficial effects in 90% of the subjects who received 0.5 mg/day of CII for 12 weeks.<sup>[5]</sup> Conversely, another 12-week study found no significant difference in benefit between three groups (placebo, 10 mg/d of CII, 1 mg/d of CII). There was, however, a higher prevalence of responders in the CII groups.<sup>[7]</sup> Researchers have noted that differences in study results may be related to the dose, species, and formulation of the CII.\*<sup>[8]</sup>

### b-2Cool<sup>®</sup>

B-2Cool is a specially developed native CII that is extracted from chicken sternums. Its manufacturing process is strictly controlled to preserve the triple helix structure of the molecule and the specific epitopes of the native protein that are thought to account for maximum effectiveness.\*

## CLINICAL APPLICATIONS

- Supports Joint Comfort and Mobility\*
- Has a Protective Effect on Endogenous Type II Collagen\*
- Modulates Immune Cell and Cytokine Activity in Joints\*

*SynovX<sup>®</sup> AI provides a proprietary blend of ingredients that specifically targets tissues, immune cells, and cytokines in joints. Type II collagen is the main structural protein in cartilage, and research suggests that low-dose, native-form type II collagen—as found in b-2Cool<sup>®</sup>—positively influences the immune response in joints via a mechanism called oral tolerization (a desensitization process). Xanthohumol, from hops, and hesperidin complement the activities of b-2Cool to deliver specialized joint support. Let SynovX AI help you stay active and moving!\**

### Pre-Clinical Study

In an experimental study performed in rats, orally administered b-2Cool (1-10 mg/kg) had positive effects on cytokine (interleukin [IL]-1 beta) production as well as comfort, as measured by a paw pressure test at days seven and 14. The lower dose displayed effectiveness at day 14. Repeated administration of the b-2Cool supported healthy spontaneous motility and preserved endogenous collagen from damage. Efficacy was comparable to that induced by 250 mg/kg/d of glucosamine.\*<sup>[9]</sup>

### Human Study

Bakilan et al demonstrated a superior effect, compared to baseline, of b-2Cool (10 mg/d) combined with a standard intervention versus the standard intervention alone. In this three-month clinical study (n = 39), significant results in comfort and mobility were achieved in the group taking the combination. The researchers concluded that “native type II collagen can afford additional benefit to conventional therapy.”\*<sup>[10]</sup>

### Hesperidin

Free radicals that are released by activated neutrophils and produced by other biochemical pathways can play a significant role in joint cartilage changes. As a citrus bioflavonoid, hesperidin (HES) has been studied for its positive effects on free radical production, COX-2 gene expression, and cytokine balance.<sup>[11-13]</sup> HES is often combined with other natural and standard joint health agents.<sup>[14,15]</sup> Animal models have demonstrated that administration of hesperidin leads to significant improvements in biochemical and histological features of experimentally challenged joint tissues.<sup>[12,16]</sup> Hesperidin administration is associated with the suppression of T-lymphocyte proliferation and IL-2 production as well as downregulation of IL-1, IL-6, and tumor necrosis factor-alpha.\*<sup>[13]</sup>

### Xanthohumol

Research suggests that hop extract, particularly xanthohumol (XN), helps support eicosanoid and cytokine balance and joint health.<sup>[17-20]</sup> Specifically, XN has been found to be superior to other hops-derived compounds (including isoxanthohumol) for inhibiting hyaluronic acid export, supporting proteoglycan and collagen homeostasis, and supporting cytokine balance in bovine chondrocytes.<sup>[18]</sup> XN appears to suppress production of nitric oxide, IL-1 beta, and TNF-alpha; induce nuclear translocation of Nrf2 (nuclear factor erythroid 2-related factor 2); and increase cellular glutathione.<sup>[21]</sup> Furthermore, XN appears to confer additional support for cytokine balance by downregulating cellular toll-like receptor 4 (TLR4) protein content.\*<sup>[22]</sup>

\*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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## SynovX® AI Supplement Facts

Serving Size: 2 Capsules



	Amount Per Serving	%Daily Value
SynovX AI Proprietary Blend Hesperidin (from <i>Citrus sinensis</i> (fruit), b-2Cool® native collagen type II, and xanthohumol (from <i>Humulus lupulus</i> )(hop cones)	485 mg	**
** Daily Value not established.		

**Other Ingredients:** Dicalcium phosphate, HPMC (capsule), microcrystalline cellulose, ascorbyl palmitate, silica, and medium-chain triglyceride oil.

**DIRECTIONS:** Take two capsules on an empty stomach, or use as directed by your healthcare practitioner. For best results, take the capsules at bedtime.

Consult a healthcare practitioner prior to use. Individuals taking medication should discuss potential interactions with their healthcare practitioner. Do not use if tamper seal is damaged.

**STORAGE:** Keep closed in a cool, dry place out of reach of children.

**DOES NOT CONTAIN:** Wheat, gluten, corn, yeast, soy, dairy products, fish, shellfish, peanuts, tree nuts, egg, ingredients derived from genetically modified organisms (GMOs), artificial colors, artificial sweeteners, or artificial preservatives.

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## REFERENCES

- Farboud A, Choy E. Serological investigation of IgG levels and subclasses in rheumatoid arthritis patients following ingestion of bovine type II collagen: results of a double blind, randomised controlled trial. *Clin Rheumatol*. 2011 Feb;30(2):193-99. [PMID: 20440528]
- Trentham DE, Dynesius-Trentham RA, Orav EJ, et al. Effects of oral administration of type II collagen on rheumatoid arthritis. *Science*. 1993 Sep 24;261(5129):1727-30. [PMID: 8378772]
- Park KS, Park MJ, Cho ML, et al. Type II collagen oral tolerance; mechanism and role in collagen-induced arthritis and rheumatoid arthritis. *Mod Rheumatol*. 2009;19(6):581-89. [PMID: 19697097]
- Barnett ML, Combitchi D, Trentham DE. A pilot trial of oral type II collagen in the treatment of juvenile rheumatoid arthritis. *Arthritis Rheum*. 1996 Apr;39(4):623-28. [PMID: 8630112]
- Ausar SF, Beltramo DM, Castagna LF, et al. Treatment of rheumatoid arthritis by oral administration of bovine tracheal type II collagen. *Rheumatol Int*. 2001 May;20(4):138-44. [PMID: 11411957]
- Barnett ML, Kremer JM, St Clair EW, et al. Treatment of rheumatoid arthritis with oral type II collagen. Results of a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum*. 1998 Feb;41(2):290-97. Erratum in: *Arthritis Rheum* 1998 May;41(5):938. [PMID: 9485087]
- Sieper J, Kary S, Sørensen H, et al. Oral type II collagen treatment in early rheumatoid arthritis. A double-blind, placebo-controlled, randomized trial. *Arthritis Rheum*. 1996 Jan;39(1):41-51. [PMID: 8546737]
- Choy EH, Scott DL, Kingsley GH, et al. Control of rheumatoid arthritis by oral tolerance. *Arthritis Rheum*. 2001 Sep;44(9):1993-97. [PMID: 11592359]
- Di Cesare Mannelli L, Maresca M, Micheli L, et al. Low dose chicken native type II collagen is active in a rat model of osteoarthritis. *Osteo Int*. 2015;26(1):P366. [on file]
- Bakilan F, Armagan O, Ozgen M, et al. Effects of native type II collagen treatment on knee osteoarthritis: a randomized controlled trial. *Eurasion J Med*. 2016;48:95-101. [on file]
- Hirata A, Murakami Y, Shoji M, et al. Kinetics of radical-scavenging activity of hesperetin and hesperidin and their inhibitory activity on COX-2 expression. *Anticancer Res*. 2005 Sep-Oct;25(5):3367-74. [PMID: 16101151]
- Umar S, Kumar A, Sajad M, et al. Hesperidin inhibits collagen-induced arthritis possibly through suppression of free radical load and reduction in neutrophil activation and infiltration. *Rheumatol Int*. 2013 Mar;33(3):657-63. [PMID: 22527139]
- Li R, Li J, Cai L, et al. Suppression of adjuvant arthritis by hesperidin in rats and its mechanisms. *J Pharm Pharmacol*. 2008 Feb;60(2):221-28. [PMID: 18237470]
- Ahmed YM, Messiha BA, Abo-Saif AA. Protective effects of simvastatin and hesperidin against complete Freund's adjuvant-induced rheumatoid arthritis in rats. *Pharmacology*. 2015;96(5-6):217-25. [PMID: 26345515]
- Natural Medicines. Hesperidin. <https://naturalmedicines.therapeuticresearch.com/databases/health-wellness/professional.aspx?productid=1033>. Accessed October 18, 2016.
- Kawaguchi K, Maruyama H, Kometani T, et al. Suppression of collagen-induced arthritis by oral administration of the citrus flavonoid hesperidin. *Planta Med*. 2006 Apr;72(5):477-79. [PMID: 16557465]
- Hougee S, Faber J, Sanders A, et al. Selective inhibition of COX-2 by a standardized CO2 extract of *Humulus lupulus* in vitro and its activity in a mouse model of zymosan-induced arthritis. *Planta Med*. 2006 Feb;72(3):228-33. [PMID: 16534727]
- Stracke D, Schulz T, Prehm P. Inhibitors of hyaluronan export from hops prevent osteoarthritic reactions. *Mol Nutr Food Res*. 2011 Mar;55(3):485-94. [PMID: 20848398]
- Gao X, Deeb D, Liu Y, et al. Immunomodulatory activity of xanthohumol: inhibition of T cell proliferation, cell-mediated cytotoxicity and Th1 cytokine production through suppression of NF-kappaB. *Immunopharmacol Immunotoxicol*. 2009;31(3):477-84. [PMID: 19555200]
- Cho YC, Kim HJ, Kim YJ, et al. Differential anti-inflammatory pathway by xanthohumol in IFN-gamma and LPS-activated macrophages. *Int Immunopharmacol*. 2008 Apr;8(4):567-73. [PMID: 18328448]
- Lee IS, Lim J, Gal J, et al. Anti-inflammatory activity of xanthohumol involves heme oxygenase-1 induction via NRF2-ARE signaling in microglial BV2 cells. *Neurochem Int*. 2011 Feb;58(2):153-60. [PMID: 21093515]
- Peluso MR, Miranda CL, Hobbs DJ, et al. Xanthohumol and related prenylated flavonoids inhibit inflammatory cytokine production in LPS-activated THP-1 monocytes: structure-activity relationships and in silico binding to myeloid differentiation protein-2 (MD-2). *Planta Med*. 2010 Oct;76(14):1536-43. [PMID: 20309792]

Additional references available upon request

All XYMOGEN® Formulas Meet or Exceed cGMP Quality Standards.

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