

TRIPLE JOINT HEALTH DEFENSE WITH NEM[®]





3X JOINT DEFENSE

PAIN
STIFFNESS
CARTILAGE

NEM® brand eggshell membrane has been shown in human clinical trials to help Defend healthy joints against Pain, Stiffness and Cartilage Degradation.* 1-5

Defense is key to long-term joint health for those involved in exercise activities, whether taking on a half marathon, or giving piggy-back rides to their kids in the yard. More and more health-conscious individuals feeling occasional aches and pains are looking for a natural alternative to reach for – something to use proactively that will not only support current joint stiffness, but also defend their future joint health.

The joint health market is no longer targeting Baby Boomers alone. According to *Natural Products Insider*, younger generations' interest in taking joint health products has increased as they want to continue living a healthy, active lifestyle.⁶

Nutrition Industry Executive further quotes, "Younger consumers are looking for ways to alleviate joint pain so they can keep up their normal exercise routines. And others are looking for ways to prevent themselves from having problems down the road."⁷

... interest in joint health products has increased as a protective measure versus facing expensive medical issues down the road.

Natural Products Insider

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3X JOINT DEFENSE



3X JOINT DEFENSE

DEFENDING 3 CRUCIAL AREAS OF JOINT FUNCTION

Research reveals that NEM® supplementation can help the body with the reduction of joint pain and stiffness (balancing inflammation), as well as help protect cartilage against breakdown.* No other joint health ingredient on the market can claim this triple-action effect with the published research to support it.

Despite the well-known benefits of exercise for a healthy lifestyle, frequent or intense exercise can actually create discomfort in the joints. Active, healthy people deal with exercise-induced pain, stiffness and cartilage breakdown on a daily basis. A lot of supplements attempt to combat one of these areas, but not all areas. Many ingredients require large doses and take up to a month, or even two, to work. When a joint health product is formulated using multiple ingredients in an attempt to combat these multiple aspects of joint health, the daily dosage can end up being quite large; all this in order to achieve results that may take a month or longer. Imagine the number of pills this could amount to before ever seeing results!



PAIN REDUCTION

Even minor day-to-day injuries can cause pain and discomfort in and around our joints. A new study in a healthy population shows that NEM® may help provide a rapid reduction of exercise-induced joint aches and pains in 7-10 days.* ¹ This fast-acting support has also been demonstrated in 5 other clinical trials previously published on NEM®.* ²⁻⁵



STIFFNESS REDUCTION

Often, joint stiffness is a result of inflammation around the joint. Inflammation is our body's way of isolating injured tissue so self-healing can take place, but all too often inflammation will persist and actually contribute to additional damage to joint tissue. New research also shows NEM's ability to help reduce joint stiffness in a quick 4 days.* ¹ Furthermore, prior *in vivo* and *in vitro* studies show that NEM® may promote a healthy inflammatory response.* ⁸⁻¹¹



CARTILAGE PROTECTION

NEM® takes joint support to a higher level by helping protect joint cartilage. Mechanism of action studies suggest that NEM® may help reduce cartilage degradation associated with normal wear and tear.* *In vivo* and human clinical studies demonstrate the action of NEM® in reducing levels of CTX-II, a recognized biomarker of Type II collagen degradation (the predominant collagen type found in cartilage tissue).* ^{1,10-12}

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NEM[®] 3X JOINT DEFENSE PAIN REDUCTION

Healthy People Have Joint Pain Too!

Having joint pain does not mean you have a joint-related disease. People deal daily with joint pain resulting from various activities. Pain, ranging from the feeling of stress or strain associated with overworking the tendons, ligaments and muscles surrounding joints, to the pain accompanying a sudden twisting movement can result from many activities, especially repetitive motion activities. Many who are health-conscious and exercise on a regular basis understand that being active puts stress on joints, and it is important to these individuals to find ways to naturally support the continuous healing process necessary to maintain an active lifestyle.



A daily 500mg dose reduces joint pain within **7-10 days.**

NEM[®] May Provide:



1 RAPID REDUCTION
of joint pain within 7-10 days*



2 REDUCTION
of exercise-induced joint pain*



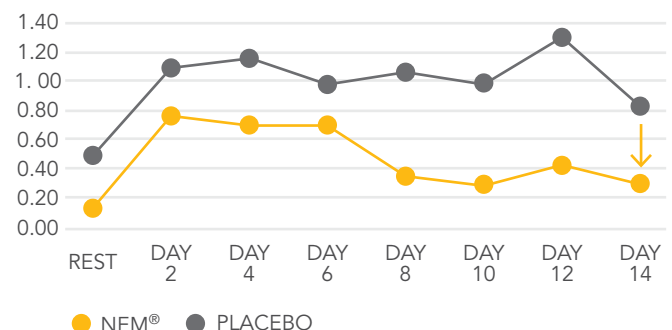
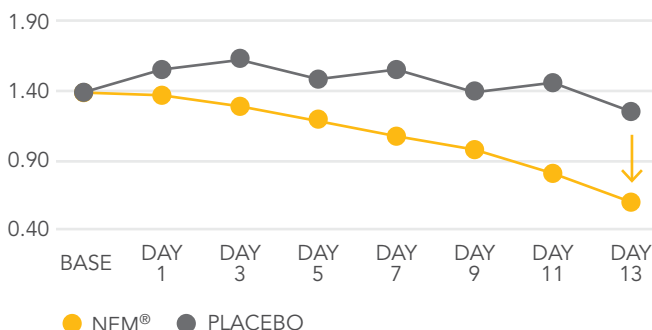
3 REDUCTION
of joint aches and pains*

A 2017 randomized, double-blind, placebo-controlled trial (RCT) in a healthy population revealed NEM's ability to reduce joint pain associated with exercise in healthy individuals in just 8 days.*¹ NEM[®] is the first dietary ingredient that has been shown to reduce exercise-induced pain in truly healthy subjects. It has also demonstrated significant reduction in pain in 5 other published clinical trials.*²⁻⁵

IMMEDIATE PAIN

Greater decrease with NEM[®]

12-HOUR PAIN



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NEM 3X JOINT DEFENSE
STIFFNESS REDUCTION

Is Your Inflammation Healthy?

Inflammation is not necessarily a bad thing; it is required for efficient self-healing to occur in the body. However, it is important that resolution of inflammation takes place in a timely manner, since uncontrolled inflammation can further damage the already stressed or injured tissue.

NEM[®] functions alongside the body to quell inflammation through modulation of the immune system's release of pro-inflammatory substances.* ⁸⁻¹¹

CLINICAL EVIDENCE

NEM[®] has demonstrated significant reduction in stiffness in four open label studies^{2,4,5} and three double-blind placebo-controlled trials.* ^{1,3} In a recently completed healthy person clinical trial, a significant reduction in exercise-induced stiffness was demonstrated in 4 days.* ¹ In addition, the largest clinical trial to date on NEM[®], an osteoarthritis RCT conducted in Turkey demonstrated a reduction in stiffness within 7 days, (in pre-publication).* Taken together, these clinical trials consistently show that a once daily 500 mg dose of NEM[®] produces a significant reduction in joint stiffness within 4-10 days.*



A daily 500mg dose
reduces joint stiffness within
4-10 days.

NEM[®] May Provide:



RAPID REDUCTION
in joint stiffness*



PROMOTION
of joint flexibility*



SUPPORT
a healthy, balanced
inflammatory response.*

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3X JOINT DEFENSE

“ Inflammation isn’t all bad, but it has to be regulated to allow healing in the body.”

Jason Theodosakis, M.D., author



IN VITRO AND IN VIVO EVIDENCE

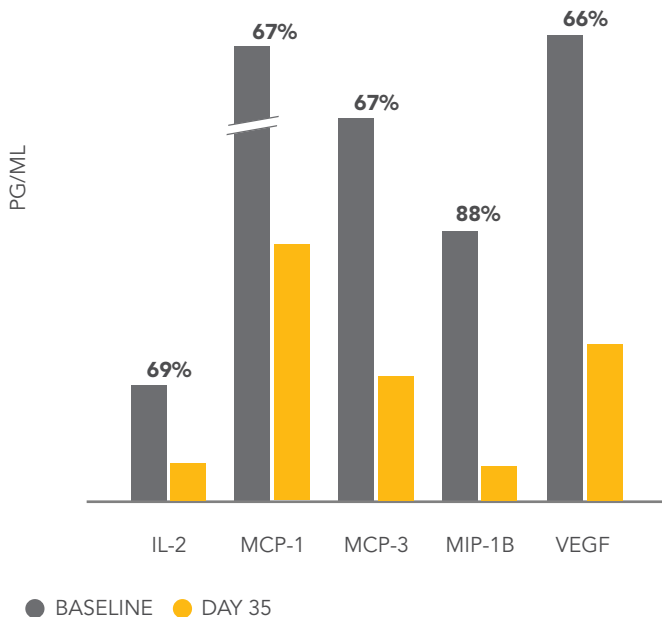
The clinical results showing improvements in flexibility and range of motion are supported by *in vitro* and *in vivo* mode-of-action studies that further elucidate how NEM® functions to modulate the inflammatory response in a positive way.* These studies consistently reveal NEM’s selective action in reducing a broad range of specific pro-inflammatory mediators, such as

TNF- α , and IL-1 β , which are often implicated in joint disorders.* ⁸⁻¹¹

NEM® down-regulates pro-inflammatory cytokines, synovial IL-1 β , and CRP.⁸⁻¹¹ NEM® has also been shown to influence the gene transcription factor NF- κ B, which plays a fundamental role in the functioning of the immune system and occurs very early in the inflammatory cascade.* ¹³

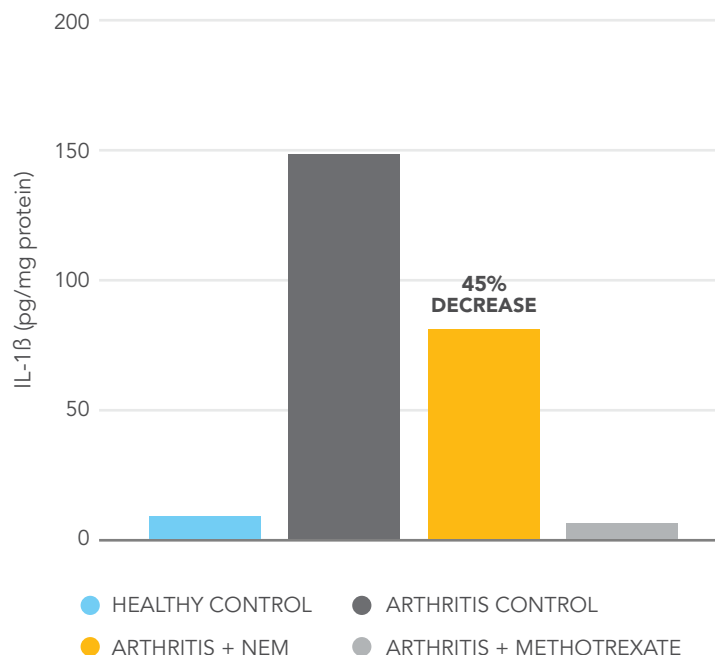
NEM DECREASES PRO-INFLAMMATORY CYTOKINES IN HEALTHY ANIMALS

PERCENT REDUCTION AT DAY 35



NEM SUPPORTS REDUCTION OF INFLAMMATORY MEDIATOR IL-1 β IN THE KNEE

45% REDUCTION



NEM® 3X JOINT DEFENSE STIFFNESS REDUCTION

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3X JOINT DEFENSE CARTILAGE PROTECTION



Healthy Joints Start with Protection!

The best way to avoid possible cartilage damage later on in life is to provide your cartilage with support long before the issues start to develop. NEM® is the first dietary ingredient to demonstrate cartilage protection in only one week in a human clinical trial conducted in healthy individuals.* This was in fact demonstrated by a reduction in a biomarker of cartilage degradation induced through exercise.*¹

CLINICAL EVIDENCE

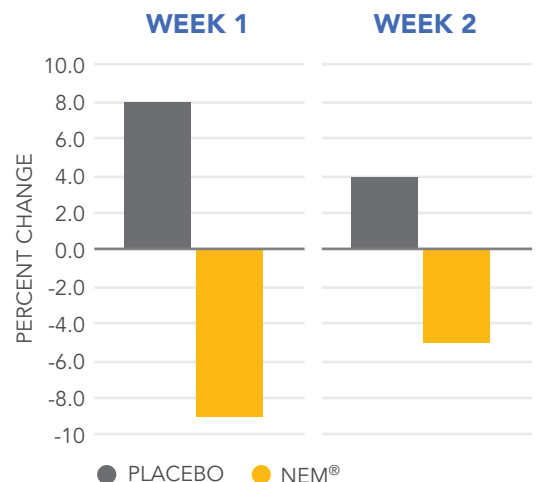
In this study, NEM® supplementation was shown to reduce post-exercise levels of CTX-II, a biomarker of cartilage degradation.* Fortunately, in most cases, the rebuilding of cartilage can keep up with the increased degradation. This is not always true for post-menopausal women because of the role of estrogen in cartilage rebuilding. For these particularly vulnerable individuals, NEM® supplementation can help provide an extra level of support.*

CTX-II levels were evaluated in post-menopausal women following 2 consecutive weeks of an exercise regimen. Post-menopausal women were specifically selected for this study because they have elevated levels of CTX-II and have more of a propensity to experience joint pain than the general population. A substantial chondroprotective effect was demonstrated from NEM supplementation through a lasting decrease in CTX-II.*¹

WHY TEST THE CARTILAGE BIOMARKER CTX-II?

CTX-II (carboxy-terminal telopeptide of Collagen Type II) is a **biomarker of cartilage degradation** that can be measured in both urine and serum and is used to assess the level of cartilage turnover. CTX-II levels are elevated in individuals where there is increased cartilage turnover, such as growing adolescents, endurance athletes, post-menopausal women and overweight individuals. The more strenuous and higher impact (jarring) the exercise, the higher the CTX-II output.

NEM REDUCES CTX-II



Net treatment effect at Week 1 was -17.2%
Net treatment effect at Week 2 was -9.9%

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CANINE EVIDENCE

The chondroprotective benefits of NEM[®] supplementation have also been manifest in a published veterinary study in dogs. In this six-week prospective, randomized, double-blind, placebo-controlled, multi-center study, 51 dogs with sub-optimal joint function were randomized to receive either orally delivered NEM[®] or a placebo. Serum levels of CTX-II in NEM-supplemented dogs were significantly reduced versus the placebo at six weeks.*¹²

IN VIVO EVIDENCE

Two rat studies have been conducted investigating NEM's chondroprotective effect. In the first study, cartilage damage in the knees mimicking osteoarthritis was induced by monosodium iodoacetate (MIA). Compared to non-arthritic rats, joint pathology was demonstrated through increases in pro-inflammatory substances and cartilage degradation markers as well as cartilage tissue damage. In arthritic rats supplemented with a human equivalent dose of NEM[®], multiple pro-inflammatory cytokines, matrix metalloproteinases (MMPs), and the cartilage degradation biomarkers, CTX-II and COMP (Cartilage Oligomeric Matrix Protein) were all significantly reduced and there was also less damage to joint cartilage.*¹⁰ In the second rat study, the effects of NEM[®] supplementation on collagen-induced arthritis in the knee and ankle were investigated. Besides demonstrating substantial improvements in ankle swelling, pannus formation, cartilage damage and bone resorption compared to the arthritic controls, NEM[®] supplementation also produced significant reductions in synovial IL-1 β and in CTX-II, COMP and alpha-2-macroglobulin (A2M).*¹¹

“ This is breakthrough research using CTX-II, which showed NEM's ability to reduce actual breakdown. ”

Jason Theodosakis, M.D., author

NEM[®] May Provide:

1

REDUCTION

in cartilage degradation associated with normal wear and tear as shown by mechanism of action studies*

2

SIGNIFICANT SUPPORT

for overall joint health*

3

KEY NUTRIENTS

found in healthy joint cartilage including glycosaminoglycans (chondroitin & hyaluronic acid), collagen, and peptides*



“AVERAGE” ARTHRITIS CONTROL KNEE

Joint space width (white space) is substantially reduced in the arthritic control knee.



“AVERAGE” NEM TREATED KNEE

Cartilage (dark purple) is substantially thicker in the NEM-treated knee.

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CLINICAL STUDIES

	N	PAIN	STIFFNESS
OA RCT Trial (Turkey) ^{pre-publication}	166	30 Days	7 Days
Healthy RCT Trial (US) ^{pre-publication}	60	8 Days	7 Days
Open Label #1 (US) ⁴	11	30 Days	ROM 7 Days
Open Label #2 (US) ⁴	28	7 Days	N/A
OA RCT Trial (US) ⁵	67	10 Days	10 Days
OA Open Label (Germany) ⁶	44	10 Days	30 Days
OA Open Label (Italy) ⁷	25	10 Days	10 Days
Healthy RCT (Canada) ^{unpublished}	60	30 Days	N/A



#1 Most Read manuscript in this journal all-time **#2** Most Read manuscript in this journal all-time
#5 Most Read manuscript in this journal all-time

REFERENCES

- Ruff KJ, Morrison D, Duncan SA, Back M, Aydogan C and Theodosakis J. Beneficial Effects of NEM® Brand Eggshell Membrane Versus Placebo in Exercise-induced Joint Pain, Stiffness & Cartilage Turnover in Healthy, Post-menopausal Women. (pre-publication)
- Ruff KJ, DeVore DP, Leu MD and Robinson MA. (2009) Eggshell Membrane: A Possible New Natural Therapeutic For Joint & Connective Tissue Disorders. Results From Two Open-label Human Clinical Studies. *Clinical Interventions in Aging*, 4:235-240.
- Ruff KJ, Winkler A, Jackson RW, DeVore DP and Ritz BW. (2009) 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*, 28:907-914.
- Danesch U, Seybold M, Rittinghausen R, Treibel W and Bitterlich N. (2014) NEM Brand Eggshell Membrane Effective in the Treatment of Pain Associated with Knee and Hip Osteoarthritis: Results from a Six Center, Open Label German Clinical Study. *Journal of Arthritis*, 3(3):136.
- Brunello E and Masini A. (2016) NEM® Brand Eggshell Membrane Effective in the Treatment of Pain and Stiffness Associated with Osteoarthritis of the Knee in an Italian Study Population. *International Journal of Clinical Medicine*, 7:169-175.
- Celeste Sepessy: Bending Backward. *Natural Products Insider* (January 2014). (4):1-4-12.
- Steber C: Joint Health for the Young. *Nutrition Industry Executive* (July 2014) 07:08.
- Benson KF, Ruff KJ and Jensen GS. (2012) Effects of Natural Eggshell Membrane (NEM) on Cytokine Production in Cultures of Peripheral Blood Mononuclear Cells: Increased Suppression of Tumor Necrosis Factor- α Levels After *In Vitro* Digestion. *Journal of Medicinal Food*, 15(4):360-368.
- Ruff KJ and DeVore DP. (2014) Reduction of pro-inflammatory cytokines in rats following 7-day oral supplementation with a proprietary eggshell membrane-derived product. *Modern Research in Inflammation*, 3(1):19-25.
- Sim BY, Bak JW, Lee HJ, Jun JA, Choi HJ, Kwon CJ, Kim HY, Ruff KJ, Brandt K and Kim DH. (2015) Effects of natural eggshell membrane (NEM) on monosodium iodoacetate-induced arthritis in rats. *Journal of Nutrition and Health*, 48(4):310-318.
- Wedekind KJ, Ruff KJ, Atwell CA, Evans JL and Bendele AM. (2016). Beneficial Effects of Natural Eggshell Membrane (NEM) on Multiple Indices of Arthritis in Collagen-Induced Arthritic Rats. *Modern Rheumatology*, 1-38.
- Ruff KJ, Kopp KJ, Von Behrens P, Lux M, Mahn M and Back M. (2016) Effectiveness of NEM® brand eggshell membrane in the treatment of suboptimal joint function in dogs: a multicenter, randomized, double-blind, placebo-controlled study. *Veterinary Medicine: Research & Reports*, 7:113-121.
- Ruff KJ, Durham PL, O'Reilly A and Long FD. (2015) Eggshell membrane hydrolyzates activate NF- κ B in vitro: possible implications for in vivo efficacy. *Journal of Inflammation Research*, 8:49-57.



NEM[®] 3X JOINT DEFENSE GENERAL INFORMATION

KEY CHARACTERISTICS:

- **Appearance:** Off-white to tan powder
- **Taste Profile:** Mild
- **Odor Profile:** Mild
- **Particle Size, Retained on #60 Mesh:** ≤5%
- **Tapped density:** ≥0.7 g/cc
- **Loose density:** ≥0.5 g/cc
- **Stability:** Stable under normal room temperature conditions
- **Shelf life:** 3 years
- **Possible Applications:** Capsules, tablets, powder mixes, sachets, gels, gummies, chewables, effervescent tablet

KEY BENEFITS

- **Fast-acting**
- **Small daily dose (500 mg)**
- **Made in the USA**
- **Manufactured in NSF-certified GMP facilities**
- **Renewable, Sustainable**
- **Traceable**
- **Safe (Self-affirmed GRAS)**
- **Non-GMO**
- **Halal & Kosher certified**
- **Shellfish free**

SUGGESTED CLAIMS:

PAIN:

- NEM[®] may help provide a rapid reduction of joint pain within 7-10 days*
- NEM[®] may help reduce exercise-induced joint pain*
- NEM[®] may help reduce joint aches and pains*

STIFFNESS:

- NEM[®] may help promote joint flexibility*
- NEM[®] may help reduce joint stiffness*
- NEM[®] supports a healthy, balanced inflammatory response.*

CARTILAGE:

- Mechanism of action studies suggest that NEM[®] may help reduce cartilage degradation associated with normal wear and tear*
- NEM[®] helps support joint health*
- NEM[®] naturally contains many of the same key nutrients found in healthy joint cartilage including glycosaminoglycans (chondroitin & hyaluronic acid), collagen, and peptides*

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