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Joint Health for Every Body

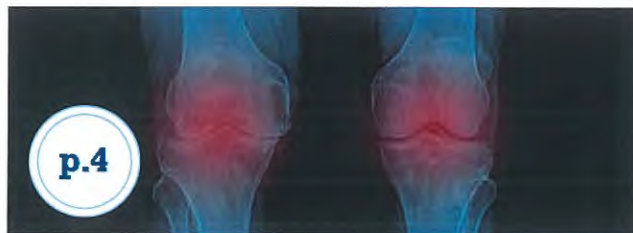
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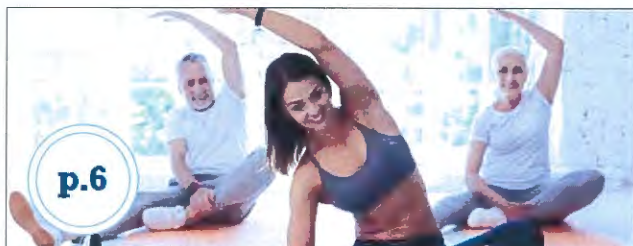
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p.4

Viewpoint: It's Such a Pain in the ...



p.6

Joint Health Ingredients: Keeping the Body Mobile

To find success in the joint health arena, brands need to identify the right ingredient or combination of ingredients, with proven efficacy to meet consumer demands, advises **Ginger Schlueter**.



p.17

Ingredients With Anti-Inflammatory Properties May Help Support Joint Health

From curcumin and omega-3s to ginger and Brahmi, many ingredients demonstrate anti-inflammatory mechanisms to help support joint health. **Karen Butler** explores the latest research.



p.26

Widening the Arena for Soft Tissue and Joint Health Supplements

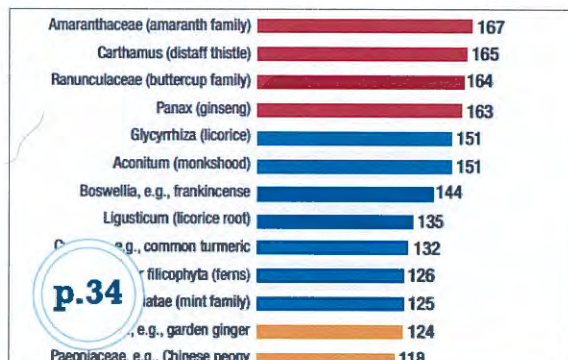
Melissa Kvidahl Reilly, National Enzyme Co., details the market for joint health products, noting the need for joint support beyond aging and senior consumers.



p.29

Joint Health Business Trends

Sudhir Ahluwalia, business consultant, reviews the business of joint health, including merger and acquisition (M&A) activity within the space.



p.34

Intellectual Property Trends in Joint Health/ Inflammation Products

A review of patent and trademark filings for joint/inflammation products by **Andreas Baltatzis** and **Gideon Eckhouse**, KramerAmado PC, indicates several category trends, including a large increase in patent filings in China for joint support nutritional products.



p.40

Takeaways for Your Business

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It's Such a Pain in the ...

Nick Foles

Trying to emulate ~~Tom Brady~~. Chasing a toddler around all day. Carrying luggage up and down subway stairs during a trip to the Big Apple. Playing guitar for hours on end. Tippy-typing away for five days straight at work. Painting a ceiling or crown molding. Playing an extra set of tennis. Running an extra mile. Walking from the ticket counter to an airline gate. Getting out of bed. The list goes on. Joints can suffer inflammation following any number of activities, seemingly strenuous or not.



In fact, the joints and surrounding soft tissue can all deliver acute pain and discomfort from inflammation due to overuse and general wear and tear. Managing such consequences is not just a pastime of old people—although aging can accelerate joint problems. The market is growing for nutritional solutions to ease inflammation and restore function to ailing joints and associated structures for consumers of all ages, activity levels and outlooks.

As such, this special Digital Magazine reviews the latest research studies on dietary ingredients for joint health, with an emphasis on inflammation control. Consumers are looking to not just assuage pains, but also to increase and maintain range of motion and flexibility to continue to live active lives going forward. And the options span beyond the staples glucosamine, chondroitin, **methylsulfonylmethane (MSM)** and hyaluronic acid (HA) into a host of herbal and specialty ingredients such as curcumin, boswellia, ginger, ashwagandha, omega-3 fatty acids and enzymes.

From a business point of view, joint and inflammation ingredients are being delivered in a range of food, beverage and supplement formats sold in an equally wide range of retail channels. A shift in the joint market from staples to newer herbal and specialty ingredients has created opportunities for small and medium companies, especially those in localized and niche segments. Globally, intellectual property (IP) trends data show innovation in the joint market may be flat in most countries, including the colossal United States, but is rising sharply in China due to government incentives.

Lean in to this special issue for all the latest market and ingredient information that can help your joint health project be successful and not a pain in the ...

Flexibly Yours,

A handwritten signature in blue ink that reads "Steve Myers".

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HEALTHY JOINTS ACTIVE LIFE

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The logo for OptiMSM, featuring the brand name in a white serif font inside a white oval shape, set against a dark blue background.

Joint Health Ingredients: Keeping the Body Mobile

by Ginger Schlueter

INSIDER's Take

- To find success in the joint health arena, brands need to identify the right ingredient or combination of ingredients with proven efficacy.
- Consumers seek alternative delivery formats for joint health products such as gels, liquid shots and functional foods and beverages.
- Joint health ingredients include popular options such as all types of collagens, egg shell membrane and MSM, and newer ingredients such as deer bone extract.

The joint health supplements industry seems hyper-focused on the aging population, as people are living longer and striving to retain mobility for as long as possible. This is not without good reason.

The U.S. Census Bureau gives a glimpse into the future with the latest population projections estimating by 2035, adults 65 and older will outnumber children for the first time in U.S. history. People ages 65 and over are estimated to number 78 million and children under age 18, 76.4 million. Beginning in 2030, all Boomers will be older than 65 and will make up 21 percent of the population, up from 15 percent today.

The same report from the bureau noted Japan has the world's oldest population with one in four people at least age 65 and Western European countries—Germany, Italy, France and Spain—have populations older than that of the United States. With Americans having fewer children and a longer life expectancy, the United States is aging.

In addition, the world is moving at a faster pace as people of all ages, globally, are adopting more active lifestyles, increasing the desire for healthy joints to sustain mobility. According the U.S. Centers for Disease Control and Prevention (CDC), in 2014, 14.6 million Americans ages 18 and over said they battled severe joint pain; today, that number is almost 15 million. "Consumers want products that improve their health, not products that mask their symptoms," explained Tim Hammond, vice president sales & marketing, Bergstrom Nutrition.

Joint health supplements are for everyone, no matter the age, and the market for joint health ingredients is steadily growing. "Many people don't realize maintaining joint health is not just a concern for the aging population, but for everyone," said Nena Dockery, technical services manager, Stratum Nutrition. The global bone and joint health ingredients market is expected to reach US\$3.3 billion by the end of 2023, growing at a compound annual growth rate (CAGR) of 6.4 percent, according to Mordor Intelligence.

Beginning in 2030, all Boomers will be older than 65 and will make up **21%** of the population, up from **15%** today.

Joint Health Consumer Trends

For companies looking to get their share of the joint health market, identifying the right ingredient or combination of ingredients offering efficacy based on scientific proof is key, along with



IN THIS ISSUE Viewpoint **p.4**

Ingredients **p.17**

Table of Contents **p.2**

meeting additional consumer preferences for joint health products. In general, consumers seek custom formulations for joint health with ingredients shown safe for long-term usage, according to Dockery. Playing into this is a proactive, preventive, custom approach to joint health, “combining ingredients to enhance desired joint health benefits,” said Oliver Wolf, head of B2B marketing, global, GELITA.

Aging and active populations are looking toward natural solutions to support range of motion, fluidity and flexibility of joints, said Samantha Ford, business development director, AIDP.

A small, once daily dose of ingredients with well-documented, broad-spectrum safety profiles verified by toxicology testing and ingredient efficacy, and backed by robust clinical trials appeals to older consumers, explained Juliana Erickson, senior marketing manager, Lonza Consumer Health & Nutrition. It’s through robust testing and trials that brands build trust and confidence with the healthy aging populations as well as health care practitioners, Erickson continued.



Consumers seek custom formulations for joint health with ingredients shown safe for long-term usage, according to Nena Dockery, technical services manager, Stratum Nutrition

Finally, it would be amiss not to mention that consumers are seeking alternative delivery formats from the “currently popular capsules and tablets,” said Lisette van Lith, global director Peptan®, Rousselot. As consumers seek healthier lifestyles, they demand healthier, on-the-go food and beverages to integrate into and accommodate their busy lives. This should encourage joint health formulators to escape the typical delivery formats and create new ways to consume joint health ingredients in the form of functional foods and beverages, liquid shots and gels.

Joint Health Ingredients

For the body to move freely in multiple directions, allowing a person to walk, bend their knees and turn their heads, for example, synovial joints must be healthy as these joints “provide the mechanism through which smooth movement can occur between bones,” Dockery explained. Synovial joints have a cavity encased by fibrous, connective tissue, forming the articular capsule. Inside this capsule is the synovial membrane, which produces hyaluronic acid (HA)-rich fluid that lubricates joints and reduces friction, allowing joint bones to glide smoothly over each other, she continued. Surrounding synovial joints are bones, muscles and ligaments, all of which provide additional joint support and stability.

Joint Health Ingredients

Important to healthy joints is healthy cartilage, which allows “perfect sliding between bones with very little friction, and its properties of elasticity and resistance make it important for cushioning and distributing pressure on bones,” van Lith said.

According to Wolf, healthy cartilage is 2 to 4 mm thick and composed of a dense, extracellular matrix with sparse distribution of chondrocytes, a type of highly specialized cells found in healthy cartilage consisting of water, collagen (secreted by these cells), proteoglycans (with glucosaminoglycans [GAGs] attached) and other noncollagenous proteins and glycoproteins. High pressure and mechanical strain can break down cartilage, causing pain and joint mobility issues, he continued.

Additionally, as humans age, collagen production slows and can lead to joint discomfort, Erickson said. Therefore, supplementing with various types of collagens can increase overall joint health by supporting healthy cartilage.

Collagen peptides—made up of the amino acids glycine, proline, hydroxyproline and arginine—may assist in cartilage health. Used as an ingredient, collagen peptides have been shown to support the healthy functioning of the musculoskeletal system: protecting joints and reducing discomfort,¹ supporting bone health,² promoting muscle mass, and protecting joints and reducing discomfort.³

Research showed bioactive collagen peptides (BCP as FORTIGEL®, from GELITA) was absorbed intestinally and accumulated in cartilage, leading researchers to conclude ingestion of BCP stimulates an increase of cartilage tissue metabolism.⁴ After oral administration, these peptides enter the bloodstream intact and accumulate in joint cartilage, Wolf explained.

Last year, the use of BCP (as FORTIGEL) was evaluated in reducing pain in athletes with functional knee problems during sport. During the study, athletic subjects ingested 5 g/d of BCPs or placebo for 12 weeks.⁵ Pain intensity during activity was evaluated by attending physicians using a visual analogue scale (VAS), with supplementation resulting in statistically significant improvements in activity-related pain intensity compared to the placebo group.



Collagen peptides—made up of the amino acids glycine, proline, hydroxyproline and arginine—may assist in cartilage health.



Type I collagen peptides promote cohesion, elasticity and regeneration of connective tissues while promoting overall joint health and mobility, van Lith said. In a clinical trial (using Peptan, from Rousselot), 94 elderly women with knee joint problems resulted in a statistically significant decrease in joint pain and improvement of stiffness after a six-month intake of type I collagen peptides.⁶

Oral consumption of hydrolyzed (broken down in water) type 1 collagen (hCol1) has been reported to reduce pain in human OA and support positive influence on chondrocyte function. Male mice with early to mid-stages of OA degeneration were given bovine hCol1 (as Peptan) incorporated into hazelnut cream (Nutella[®]) each morning for 16 weeks, so that 150 mg of the mixture would deliver either a low dose (3.8 mg) or high dose (38 mg).⁷ Researchers drew blood at various intervals to ensure absorption of hCol1 and after the study concluded; close examination of cartilage architecture, chondrocyte populations and synovial change showed significant chondroprotective effects in injured joints of the mice. These findings could conclude daily oral consumption of hCol1 is joint protective and disease modifying in OA joints.

Undenatured (not processed by high heat or chemicals) type 2 collagen is proposed to work in the gut with the immune system to help the body build cartilage, Erickson said. Studies have shown undenatured type 2 collagen (as UC-II, from Lonza) helped improve joint comfort, mobility and flexibility in people with OA.⁸

In a recent study, UC-II was orally administered to 10 male rats starting immediately after surgery to repair a partial medial meniscectomy tear (PMMT) at 0.66 mg/kg and continued for a period of eight weeks.⁹ UC-II preserved the weight-bearing capacity of the injured leg, preserved integrity of the bone and limited deterioration of articular cartilage, showing clinically relevant daily dosages of UC-II immediately after surgery can improve mechanical function and prevent excessive deterioration of articular cartilage.



Studies have shown undenatured type 2 collagen (as UC-II, from Lonza) helped improve joint comfort, mobility and flexibility in people with osteoarthritis.

Rousselot's Peptan[®] IIm, a collagen type 2 matrix, was developed to promote multiple joint health benefits, including reducing inflammation. The ingredient contains a matrix of hydrolyzed type 2 collagen peptides and GAGs, which mimics the body's natural composition of the cartilage matrix.

In a recent in vivo study in mice with and without post-traumatic OA, three weeks of consuming Peptan IIm promoted lubrication in joints through stimulation of proteoglycan synthesis in chondrocytes, enabling easier joint movement.¹⁰



In unpublished in vivo studies, Peptan IIm supplementation helped prevent joint problems by minimizing local inflammation, protecting the cartilage from degeneration and stimulating chondrocytes to produce lubricating matrix. The in vivo studies examined post-traumatic OA induced by injury and obesity-induced OA. According to van Lith, “The first condition mimics the disease as it develops in humans after injury or during aging. The second is highly relevant in light of the global epidemic of overweight and obesity that is clearly linked to an increased incidence of joint problems.”

She continued, “The state-of-the-art animal models that were used allowed researchers to assess the cartilage matrix and cells, as well as the local inflammation of the synovial membrane in lean and obese mice suffering from knee osteoarthritis induced by surgical injury. The animals treated preventatively with Peptan IIm showed a reduced degeneration of the cartilage and a higher proteoglycan production by the chondrocytes. Importantly, the levels of the local synovial inflammation were significantly reduced compared to the untreated control groups.”

AIDP’s KollaGen II-xs™, a type 2 collagen produced from avian sternum via a proprietary, solvent-free technology, and containing 50 to 70 percent collagen type 2 plus chondroitin, glucosamine and HA, supports range of motion, flexibility and overall joint comfort.

A 30-day, randomized, controlled trial of 15 subjects receiving 1,500 mg/d of KollaGen II-xs demonstrated efficacy by improving essential symptoms in individuals suffering from joint diseases, including range of motion, general pain and muscle strength.¹¹

A few other popular ingredients make strong statements for joint health in the market. Commonly disposed of as waste by egg processing industries,¹² avian eggshells and membranes have a high content of bioactive components that have received increasing attention for joint health applications.

In a 12-week, randomized, double-blind, placebo-controlled crossover study, 22 participants consumed 450 mg/d of hydrolyzed water-soluble egg membrane (WSEM as BiovaFlex®, from Biova LLC and distributed exclusively in the United States by Stauber), resulting in improved joint function as indicated by range of motion and VAS.¹³

Another branded eggshell membrane, NEM® from Stratum Nutrition, which delivers three collagen types, chondroitin sulfate, keratin sulfate and HA, has been shown to decrease the cartilage-degradation biomarker CTX-II, Dockery said. Blood or urine is tested to measure the presence of type 2 collagen fragments, giving a reliable rate of cartilage turnover. “Elevated turnover rates are normal during periods of growth in children and endurance athletes because breakdown is balanced by cartilage rebuilding,” Dockery concluded.

In an in vivo trial to investigate anti-arthritis activity, NEM was administered at 52 mg/kg, 200 mg/kg and 400 mg/kg to rats with arthritis induced by monosodium iodoacetate.¹⁴ The study showed a decrease in patella cartilage, synovial membrane and transformation of fibrous tissue, resulting in significant anti-arthritis



activity when taking NEM. A later randomized, double-blind, placebo-controlled study was conducted at veterinary clinics to evaluate efficacy, safety and tolerability of NEM in dogs. Fifty-one dogs received either oral NEM at approximately 13.5 mg/kg/d or placebo for six weeks, leading to a significant reduction of joint pain and improved joint function in the NEM-supplemented dogs.¹⁵ In a final study, NEM was evaluated for its ability to reduce exercise-induced cartilage turnover or alleviate joint pain or stiffness directly following exercise 12 hours afterward. Sixty healthy, postmenopausal women received 500 mg/d of NEM or placebo for two consecutive weeks while performing 50 to 100 steps per leg on alternating days. Supplementation with NEM resulted in rapid improved recovery from exercise-induced joint pain on day seven with no serious adverse events.¹⁶

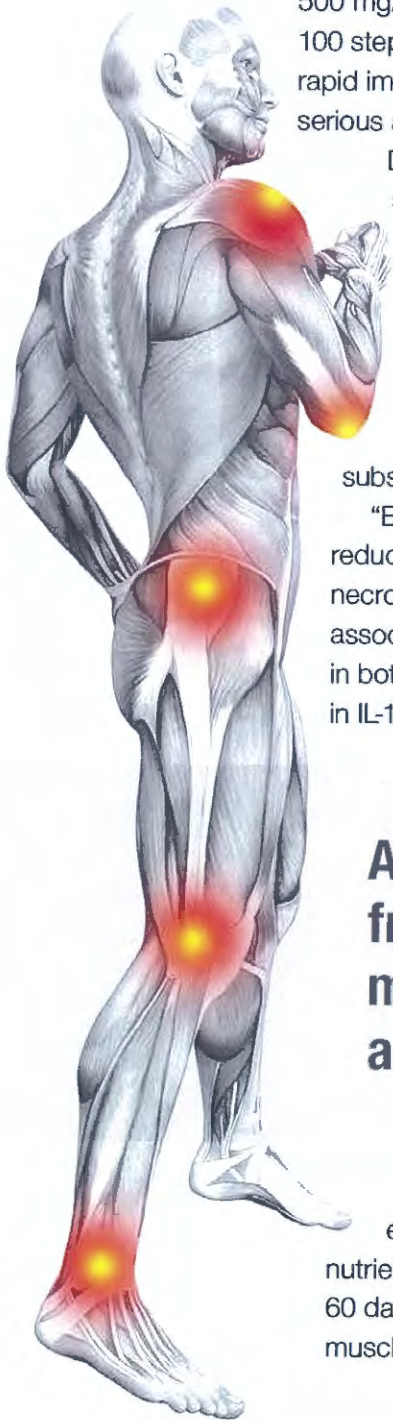
Dockery said research on NEM has almost exclusively focused on joint support. "One of the areas that was measured in the NEM clinical trials was inflammation in and around joint tissues, indicated by joint stiffness and limited range of motion.^{17,18,19,20,21} Subjects in these studies included individuals with all levels of joint concerns, from those with more severe osteoarthritis (pre-publication study) to post-menopausal women with no joint pain in whom pain and stiffness were induced through exercise."

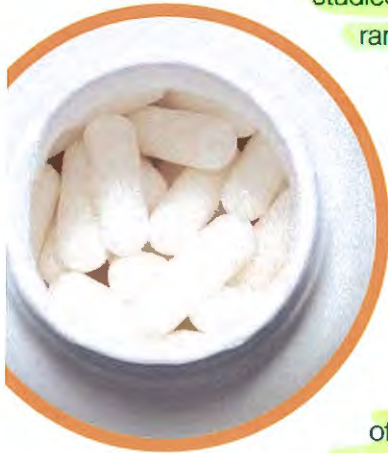
NEM functions through controlling the secretion of pro-inflammatory substances, including cytokines and matrix metalloproteinases (MMPs).^{22,23,24,25}

"Benefits that are particularly relevant to joint health include demonstrated reductions in the levels of the two pro-inflammatory cytokines, TNF- α [tumor necrosis factor alpha] and IL-1 β [interleukin-1 beta], which are most often associated with joint disorders," Dockery said. "These reductions were shown in both in vitro trials and animal studies, and included data showing a decrease in IL-1 β , not only in serum, but more significantly, in joint synovial fluid."

A new ingredient (TendoGuard™, from AIDP) combines avian eggshell membrane and sternum cartilage for a comprehensive blend of nutrients.

Another new ingredient (TendoGuard™, from AIDP) combines avian eggshell membrane and sternum cartilage for a comprehensive blend of nutrients. In a single-center observational study, 750 mg/d of TendoGuard for 60 days in human subjects improved range of motion, general pain and muscle strength.²⁶





Also in the joint health rotation is methylsulfonylmethane (MSM), which has been studied for its impact on inflammation and joint function. A double-blind, randomized, controlled trial was conducted on a total of 147 patients with knee OA who were divided into three groups: the GC group received daily 1,500 mg of glucosamine, 1,200 mg of chondroitin sulfate and 500 mg of saccharum lactis; the GCM group received daily 1,500 mg of glucosamine, 1,200 mg of chondroitin sulfate and 500 mg of MSM (as OptiMSM® by Bergstrom Nutrition); and a placebo group received three matching capsules.²⁷ VAS and Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index scores were measured before treatment, then at weeks four, eight and 12 after treatment. The study determined reduced pain scores in the intervention groups, demonstrating the addition of 500 mg of MSM with glucosamine and chondroitin optimized reduction of pain and improvement of physical function.

Results from a double-blind, placebo-controlled study of 100 subjects with hip or knee OA showed distilled MSM significantly improved all WOMAC subscale and SF-36 daily living scores (a measure of patient health perception) after 26 weeks of supplementation.²⁸

Rodney Benjamin, director of research and development (R&D) and technical support for Bergstrom Nutrition, stated, "While MSM's mechanism of action is not fully understood, *in vitro* studies, along with both animal and human trials, have shown MSM helps mitigate the oxidative stress that can lead to chronic inflammation.^{29,30,31} Additional studies have also shown MSM inhibits pro-cytokine expression³² and the activation of nuclear factor kappa B (NF- κ B)."³³

An *in vitro* study evaluating the effect of OptiMSM on tissue components from the knee joint reduced the expression of inflammatory markers tumor TNF- α and IL-1 by 33 percent and 29 percent.³⁴

A couple of lesser-known joint health ingredients are gaining traction or just making their mark in the market.

Boswellia serrata is an herbal extract traditionally used in India for joint health. Recent studies have investigated its ability to address joint inflammation. In a study of people suffering from Achilles tendonitis or epicondylitis, supplementation with a specialty combination of a boswellia extract (as Casperome®, from Indena) with a formulation of sodium hyaluronate, collagen and glucosamine (Tendhyal®), reduced pain and improved the functionality of the affected area.³⁵

A randomized, double-blind, placebo-controlled study published this year evaluated 50 participants, ages 50 to 70, with knee OA and a WOMAC score less than or equal to 5.39.³⁶ Participants consumed placebo or 550 mg/d of deer bone extract (DBE) for 12 weeks, with findings of reduction in joint pain and stiffness and improved joint function for the DBE group.

"Joint health affects many people on different levels, including athletes, people with active lifestyles and people who want to maintain mobility in their senior years," van Lith said. Therefore, it's important to continue researching natural ingredients to help maintain joint health.



Ingredients With Anti-Inflammatory Properties May Help Support Joint Health

by Karen Butler

INSIDER's Take

- Short-term inflammation is a protective response, but chronic inflammation can have a negative effect on the human body.
- Persisting local inflammation of the joint is now recognized as a key driver of osteoarthritis (OA) progression.
- Ingredients such as curcumin and omega-3s have demonstrated anti-inflammatory mechanisms.

Inflammation often gets a bad rap; however, when working in tandem with the body's natural design, it can provide support against irritation, cell damage and pathogenic activity. But not all inflammation is created equal—as evidenced by its potential effects in joint health.

In a peer-reviewed study, Garry Egger, Ph.D., MPH, wrote, “For more than 2,000 years, classical inflammation has been recognized by the symptoms identified by the Roman physician Aurelius Celsus as pain (dolor), redness (rubor), heat (calor) and swelling (tumor), with the more recent addition of loss of function (torpor).”¹

He noted inflammation is typically a short-term response to infection and injury that helps the body heal and return to homeostasis. “However, in 1993, researchers discovered a different type of prolonged, dysregulated and maladaptive inflammatory response associated with obesity,” Egger shared. This “metainflammation” differs from classical inflammation in many ways, some of which include being persistent; resulting in chronic, rather than acute, allostasis (the body's response to stressors while trying to regain homeostasis); having systemic vs. local effects; and appearing to perpetuate rather than resolve disease.

According to the Arthritis Foundation, osteoarthritis (OA) is the most common chronic condition of the joints.² Initially associated with the deterioration of cartilage, OA can affect any joint, but occurs most often in knees, hips, lower back and neck, small joints of the fingers and the bases of the thumb and big toe. As OA progresses, “In the body, an inflammatory process occurs and cytokines (proteins) and enzymes develop that further damage the cartilage,” the foundation explained.

OA affects more than 30 million Americans, and an estimated 91.2 million adults have either been medically diagnosed with some form of arthritis and/or report joint symptoms consistent with it.

From over-the-counter (OTC) ibuprofen and aspirin to a wide variety of prescription brands, nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used as an initial therapy for common inflammation. However, health complications and fatalities attributed to NSAID use in arthritis patients are reported annually in the United States.³

Osteoarthritis affects more than **30 million Americans**, and an estimated **91.2 million adults** have either been medically diagnosed with some form of arthritis and/or report joint symptoms consistent with it.





Fortunately, a host of researched ingredients is at the ready for consumers desiring alternatives to traditional NSAIDs.

Curcumin (*Curcuma longa*), which is extracted from turmeric, has been indicated as an anti-inflammatory for joint health. However, concerns have been raised about its bioavailability, which has led to the development of unique solutions and delivery systems. According to a 2017 review⁴: “Curcumin has received worldwide attention for its multiple health benefits, which appear to act primarily through its antioxidant and anti-inflammatory mechanisms. These benefits are best achieved when curcumin is combined with agents such as piperine [the major active component of black pepper], which increase its bioavailability significantly. Research suggests curcumin can help in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety and hyperlipidemia. It may also help in the management of exercise-induced inflammation and muscle soreness, thus enhancing recovery and subsequent performance in active people. In addition, a relatively low dose can provide health benefits for people that do not have diagnosed health conditions.”

A study done at St. John’s Medical College, Bangalore, India, provided clinical evidence of piperine’s role in increasing the bioavailability of curcumin.⁵ When 2,000 mg of curcumin (as C3 Complex[®], from Sabinsa) was co-administered with 20 mg of piperine (as BioPerine[®], from Sabinsa), the bioavailability of curcumin was enhanced 2,000 percent compared to bioavailability of curcumin alone at doses that were devoid of adverse side effects.



Curcumin has received worldwide attention for its multiple health benefits, which appear to act primarily through its antioxidant and anti-inflammatory mechanisms.

Indena S.p.A. uses its Phytosome[®] delivery format to help ameliorate absorption. A human clinical study indicated overall curcuminoid uptake was about 29-fold higher for Meriva[®], the company’s patented Phytosome turmeric formulation, as compared to an unformulated curcuminoid mixture.⁶

“Meriva is supported by more than 30 clinical trials demonstrating effectiveness in 10 different health conditions, showing the ability to modulate the inflammatory response,” reported Cosimo Palumbo, Indena’s marketing director. He pointed to an eight-month study involving 100 subjects with OA, where the ingredient “induced a statistically significant reduction of numerous markers of inflammation such as C-reactive protein (CRP) levels that decreased by 16-fold.”⁷

Anti-Inflammatory Ingredients

In another study of 50 individuals with OA, the treatment group took Meriva in a dose reflecting 200 mg/d curcumin.⁸ After three months, for subjects receiving Meriva, the global Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score decreased by 58 percent ($P < 0.05$); walking distance in the treadmill test was prolonged from 76 m to 332 m ($P < 0.05$); and CRP levels decreased from 168 ± 18 to 11.3 ± 4.1 mg/L in the subpopulation with high CRP. In comparison, the control group experienced only a modest improvement in the parameters. Researchers concluded Meriva was clinically effective as a complementary management tool in OA.

OmniActive Health Technologies also uses a unique method for enhancing the bioactives in its CurcuWIN. The company's UltraSOL Nutrient Delivery System converts lipophilic compounds and poorly absorbed nutrients to water-dispersible ingredients for enhanced bioavailability. In a human clinical trial, CurcuWIN increased relative absorption of total curcuminoids 46 times over standard curcumin.⁹ According to the company, the ingredient contains a minimum of 20 percent curcuminoids in the same profile as found naturally in turmeric.

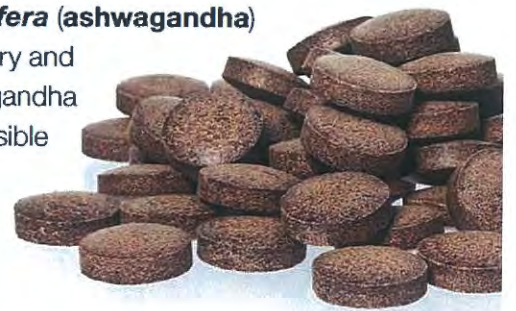
One formulation capitalizes on curcumin's potential by pairing it with other botanicals. An unpublished study examined the effects of glucosamine and chondroitin compared to Aurea Biolabs' Acujoint™, a proprietary mixture of *Curcuma longa* extract, bioavailable *Boswellia serrata* extract, *Piper nigrum* oil and *Kaempferia galanga* extract.¹⁰

In the randomized, double-blind, active-controlled and monocentric clinical study, active OA participants received 250 mg of Acujoint, or 1,500 mg of glucosamine plus 1,200 mg of chondroitin for 90 days. The Acujoint group showed greater improvement than the glucosamine/chondroitin group in WOMAC, pain, visual analogue scale (VAS) and functional ability scores, as well as LF index values and high-sensitivity (hs)CRP biomarkers.

AyuFlex® from Natreon Inc. is an aqueous extract derived from the ancient Indian Ayurvedic edible fruits of *Terminalia chebula*, offering a vegan option for joint health formulations. Backed by seven clinical studies to promote optimal joint health and reduce chronic discomfort, its mechanism of action is to inhibit the enzymes responsible for pain and inflammation. The ingredient was shown to reduce the inflammation biomarker hsCRP and support healthy joints in people with activity-dependent knee pain.¹¹

Another study of 100 subjects experiencing knee joint discomfort for at least six months found Ayuflex supported joint health, demonstrated through modified WOMAC scores, VAS and knee-swelling index (KSI).¹²

Root extracts of the adaptogen *Withania somnifera* (ashwagandha) have been studied for their potential anti-inflammatory and chondroprotective effects. One review noted ashwagandha "can inhibit cyclooxygenase (COX), the enzyme responsible for the formation of important biological mediators of inflammatory and anaphylactic reactions.^{13,14} Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain."



Anti-Inflammatory Ingredients

In a randomized, double-blind, placebo-controlled clinical study, 60 patients with knee joint pain and discomfort were given 250 or 125 mg/d of *W. somnifera* (as Sensoril®, from Natreon Inc.), or placebo.¹⁵ At the end of 12 weeks, compared to baseline and placebo, significant reductions were observed in mean modified WOMAC and KSI in the Sensoril 250 mg (P<0.001) and 125 mg (P<0.05) groups. VAS scores for pain, stiffness and disability were significantly reduced in Sensoril 250 mg (P<0.001) and 125 mg (P<0.01) groups. The Sensoril 250 mg group showed earliest efficacy, at four weeks.

Another botanical, ***Zingiber officinale***—commonly known as **ginger**—has been linked to joint health benefits, particularly in the autoimmune condition rheumatoid arthritis (RA). Brian Appell, activation marketing manager, OmniActive Health Technologies, specified, “The potent anti-inflammatory properties in the gingerols in ginger are believed to help provide protection against harmful free radicals.”¹⁶

He added, “As an anti-inflammatory, ginger has been shown to reduce the production of cytokines IL [interleukin]-1 and IL-6, and inhibit COX-2 and 5-lipoxygenase enzymes, which play a role in the inflammatory process.”¹⁷

Another root extract commonly used in Ayurveda, ***Bacopa monnieri*** (also known as **Brahmi**), acts by selectively inhibiting the COX-2 enzyme, and consequently reducing prostaglandins synthesis.¹⁸

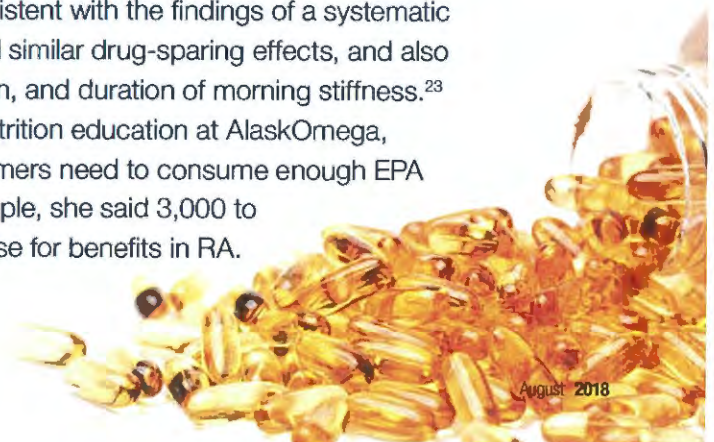
Deanne Dolnick, science director, TR Nutritionals, pointed to research that touted, “In modern biomedical studies, Bacopa has been shown in animal models to inhibit the release of the pro-inflammatory cytokines TNF- α [tumor necrosis factor-alpha] and IL-6 to aid in the treatment of arthritis.”¹⁹

The **omega-3s eicosapentaenoic acid (EPA)** and **docosahexaenoic acid (DHA)** are long-chain polyunsaturated fatty acids (PUFAs) found in fish, algae and other marine oils. Nate Matusheski, Ph.D., scientific leader, nutrition science and advocacy, at DSM Nutritional Products, stated EPA and DHA serve as biological precursors to resolvins and protectins (bioactive metabolites) that help regulate inflammatory processes.²⁰

Omega-3 supplementation has been found to lower the concentrations of pro-inflammatory eicosanoids in the bloodstream,²¹ a biological mechanism that may have implications for joint health.

A meta-analysis of randomized controlled trials (RCTs) found a decrease in NSAID use when individuals with RA were supplemented with more than 2.7 g/d of EPA and DHA for three months or longer.²² These results were consistent with the findings of a systematic review by a different research group that identified similar drug-sparing effects, and also modest beneficial effects on joint swelling and pain, and duration of morning stiffness.²³

Gretchen Vannice, MS, RDN, head of global nutrition education at AlaskOmega, cautioned dose can be a central issue, as “consumers need to consume enough EPA and DHA omega-3 for it to be effective.” For example, she said 3,000 to 6,000 mg/d of EPA and DHA is a documented dose for benefits in RA.



“Although there is not a US RDI [reference daily intake] for EPA and DHA, experts and national health organizations agree that at least 250 to 500 mg EPA and DHA is a minimum amount to prevent deficiency,” she shared. “Consumers need to know that this amount is not enough to address inflammation associated with common diseases, such as heart disease, diabetes, metabolic syndrome and obesity.

“Among the reasons that more EPA and DHA are needed is because when there is enough in tissues they are able to ‘redirect’ metabolism, thereby lessening the cause of inflammation; this is very different from OTC medications, which typically reduce the experience of pain, but not the physiological cause,” Vannice explained.

Omega-3 supplementation has been found to lower the concentrations of pro-inflammatory eicosanoids in the bloodstream, a biological mechanism that may have implications for joint health.



Hyaluronic acid (HA) is a component particularly abundant in the synovial fluid found in joint cavities. A 2016 review noted, “Randomized, double-blinded, placebo-controlled trials carried out between 2008 and 2015 have proven the effectiveness of HA for the treatment of symptoms associated with synovitis, and particularly, knee pain, relief of synovial effusion or inflammation, and improvement of muscular knee strength.”²⁴

In a randomized, placebo-controlled, double-blind clinical study, 20 subjects with knee OA took 200 mg/d of HA (as Hyabest®[J], from Kewpie Corp) and 17 consumed a placebo.²⁵

WOMAC score analysis of participants suffering from severe pain indicated the Hyabest (J) group showed significant improvement over the placebo group after eight weeks.

According to Kazunori Asaoka, marketing department manager, Kewpie Corp., the mechanism of improvement in OA is that “oral administration of Hyabest(J) modulates inflammation by upregulating suppressor of cytokine signaling-3 expression and downregulating pleiotrophin expression via toll-like receptor [TLR]-4 in intestinal epithelial cells.”²⁶

And lastly, **tomato** phytonutrients have been linked to potential benefits on bone and joint health. One study examined whether carotenoid derivatives inhibit NF-κB, as well as determining the molecular mechanism underpinning the inhibitory action.²⁷ Researchers found that lycopene preparations purified from tomato extract (from Lycored) inhibited NF-κB reporter gene activity.



When considering bone and joint formulations, Karin Hermoni, Ph.D., head of science and nutrition at Lycored, suggested, “The mechanism of action of such an effect may involve the control of inflammatory processes as well as the antioxidant properties of tomato phytonutrients. Of note, carotenoids such as lycopene act not only by quenching reactive oxygen species [ROS], but also by boosting the cell’s own antioxidant defense mechanism.”

Many additional ingredients have been researched and are available to help support inflammation in joint health—with particular opportunity in the natural products sector. 🌀

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Widening the Arena for Soft Tissue and Joint Health Supplements

by Melissa Kvidahl Reilly

INSIDER's Take

- The global bone and joint supplement market is expected to grow at a CAGR of 6.72 percent between 2017 and 2021.
- Younger consumers (those ages 18 to 24) are most likely to meet physical activity guidelines, increasing their need for joint support.
- Enzymes are the “unsung heroes” for minor exercise-induced inflammation and joint health in general.

Typically when picturing a joint health supplement consumer, Baby Boomers or their parents come to mind. With estimates that half of men and two-thirds of women over age 65 have concerns related to joint or soft-tissue health, according to arthritis.org, it's no surprise thoughts of joint health are paired with thoughts of the elderly. However, the market for supplements targeted at joint health and soft-tissue support is far greater than the senior saints journalist Tom Brokaw popularized as “the greatest generation.”

Consumers of all ages and lifestyles can benefit from a soft tissue and joint support supplement regimen, from professional or recreational athletes to teen and adult sportsters to weekend warriors simply trying to maintain health over time. Undoubtedly part of a healthy living plan, exercise does cause the body to produce an inflammatory response. Post-workout muscle soreness, for example, is a symptom of minor inflammation. This negligible, self-resolving inflammation isn't necessarily a sign of disease, since the body needs these signals to build muscle tissue post-workout. Still, consumers are looking for ways to support their joint and soft-tissue health with supplements.

According to research from Technavio, the global bone and joint supplement market is expected to grow at a compound annual growth rate (CAGR) of 6.72 percent between 2017 and 2021. And turmeric (or curcumin), which has earned superfood status thanks to its noted antioxidant properties, is on the rise with consumers experiencing occasional, minor, self-resolving inflammation. In fact, the latest Annual Survey on Dietary Supplements from the Council for Responsible Nutrition (CRN) found roughly one out of 10 supplement users takes this

herbal supplement. Other popular ingredients in the category are glucosamine, chondroitin and methylsulfonylmethane (MSM).

Enzymes, however, are the “unsung heroes” for minor exercise-induced inflammation and joint health in general, said Naeem Shaikh, Ph.D., vice president of research and innovation at National Enzyme Co. (NEC). While most



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and



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IN THIS ISSUE

Ingredients **p.17**

Business **p.29**

Table of Contents **p.2**

supplement consumers are aware of the benefits of nutritional enzymes for digestive support, supplementary enzymes for systemic use are lesser-known. As essential regulators and modulators of the inflammatory response, systemic enzymes benefit muscle recovery in a few different ways. “They decrease capillary permeability, promote optimal viscosity of the blood and dissolve fibrin, which is a protein that clots the blood,” Shaikh explained. The benefit? More blood supply to the muscles post-exercise, he said, bringing with it much-needed oxygen and nutrients. On the way out, this blood supply drives away debris for easier passage through the lymphatic system.



Nearly 70 percent of supplement users report exercising regularly, as opposed to just 59 percent of non-users who do, as reported in CRN’s annual survey.

Ultimately, Americans—and especially supplement users—understand exercise is part of a healthy lifestyle. Gym memberships have risen from 32.8 million in 2000 to 57.25 million in 2016, according to Statista. Nearly 70 percent of supplement users report exercising regularly, as opposed to just 59 percent of non-users who do, as reported in CRN’s annual survey. And it’s younger consumers (those ages 18 to 24) who are most likely to meet federal physical activity guidelines, the U.S. Centers for Disease Control and Prevention (CDC) reported in 2016. Indeed, these younger consumers shouldn’t be forgotten by formulators in the joint health and soft-tissue market. On the contrary, it seems the healthiest market will be one that caters to supplement consumers of all ages, and with a range of ingredients to support their needs and preferences.



*This article was written by Melissa Kvidahl Reilly and submitted by [National Enzyme Co.](#) Reilly is a freelance writer with 10 years of experience covering the natural products industry, from food and beverage to personal care, from research developments to market trends. Her work appears in many industry publications, including *Natural Products INSIDER*, *Food Insider Journal*, *Natural Foods Merchandiser*, *Delicious Living* and more. She lives and writes in New Jersey. She can be contacted at melissakvidahl.com.*

Joint Health Business Trends

by Sudhir Ahluwalia

INSIDER's Take

- Glucosamine/chondroitin formulations lead joint health solutions, but the trend is shifting toward plant-based ingredients.
- The shift of market share is creating new prospects for natural product ingredient suppliers and product manufacturers.
- In the growing bone and joint health market, niche companies are good candidates for acquisition.

The global bone and joint health market is estimated at US\$1.6 billion, and is forecast to exceed \$9 billion by 2017, according to data from Mordor Intelligence. A 2012 study from the U.S. Bone and Joint Initiative observed the worldwide impact of musculoskeletal conditions such as arthritis and back pain affects more than 1.7 billion people worldwide.

Aging leads to weakening of bone and joints. This makes the body more prone to bone fractures, arthritis, back and neck pain, osteoporosis and injuries. Demographics in the United States and other developed countries are particularly prone to age-related bone and joint health conditions. This aging population is one major consumer of bone and joint health products.

Athletes and gym goers also consume bone and joint health supplements to prevent bone deterioration. Calcium is the most widely used bone health ingredient. The U.S. and European markets are highly competitive and dominate the bone and joint health care market. Asia Pacific and emerging economies are the second-most important and fastest areas of growth.

The market for joint health supplements is still dominated by glucosamine and chondroitin formulations. However, plant-based ingredients and products containing turmeric, *Boswellia serrata*, tart cherry, omega-3s and other natural product-based formulations are gaining popularity.



Turmeric



Boswellia serrata



Tart Cherry



Omega-3s

Bone and joint health ingredients are being added not just in supplements, but in food and snack products. These include sweet and savory snacks, oils and fats, meat products, bakery and confectionery, dairy and frozen desserts, beverages and more.

IN THIS ISSUE Market [p.26](#)

Intellectual Property [p.34](#)

Table of Contents [p.2](#)

Not only are these products sold in health food stores and pharmacies, but also in supermarkets, national discount chain stores and online mail order catalogs. Extensively advertised on television, the internet and in print, a substantial amount of marketing dollars is spent to drive sales of wellness products.

This market includes some large suppliers globally. Synutra Inc., DuPont, Archer Daniels Midland (ADM) in the United States, Rousselot, Royal DSM NV in the Netherlands, Waitaki Bio in New Zealand and BASF SE in Germany are among the more significant players in the segment. Other companies such as Glanbia PLC, Holista Colltech Ltd., Stratum Nutrition, Bergstorm Nutrition Inc. and Gelita AG are producing and competing in the bone and joint health product market segment space, too.

Corporations are actively investing in bone health product research and manufacture. For instance, ADM now operates one of the world's largest soy isoflavone facilities, manufacturing supplement products from non-GM (genetically modified) soybean varieties. Its Novasoy brand can be found in more than 125 supplement brands all over the world.

BASF maintains four Newtrition® Labs in Europe, one in North America and another in South America, where analysis and research on dietary supplements, foods and beverages is conducted. In 2017, the company opened another Newtrition Lab in Singapore.

SPINS reported the glucosamine-chondroitin ingredients market value decreased 9.6 percent for the 52 weeks ending Nov. 27, 2016, but it continues to have the highest market share.



The market is trending and shifting to natural product-based bone/joint health solutions. These products contain ingredients like *Terminalia chebula*, collagen and others. This shift may take place at the cost of the bone/joint health supplement market leader glucosamine-chondroitin. SPINS reported the glucosamine-chondroitin ingredients market value decreased 9.6 percent for the 52 weeks ending Nov. 27, 2016, but it continues to have the highest market share.

This shift of market share is opening new prospects for natural product ingredient suppliers and product manufacturers. Most companies in this segment are small- and medium-sized. They have limited access to capital, which often constrains growth. They often operate in niche and localized markets; however, many of them offer unique products.

Growth is impeded by lack of streamlined, best-in-class business processes, business and marketing networks, institutional capability and technology support systems. This makes it difficult for small units to rapidly expand market footprint, improve production efficiency and obtain higher margins.



In a growing market like bone and joint health, niche companies are good candidates for acquisition. Big corporations often expand, buying market share, innovation capability and niche market access. The growth in bone and joint health makes the segment conducive to a high level of mergers and acquisitions (M&A) activity.

Corporations are typically always on the lookout for acquisition candidates. They not only look at the target's balance sheet, but also its internal company processes, innovation potential, niche market strengths, and any other unique selling proposition that can be quickly leveraged and scaled.

Promoters of unique, small companies can substantially benefit in such a business scenario, but must prepare to leverage opportunities. At the outset, the balance sheet should be kept free from debt. The innovation capacity of the company needs to be kept up and continuously nourished. Further, its position in its niche market should be maintained. Companies with e-commerce linkages and artificial intelligence (AI) solutions integrated into product marketing infrastructure in the evolving technology scenario could have an added advantage.

The bone and joint health market segment—whether supplements or food and health care products—is in a sweet spot. Asia Pacific is exhibiting strong growth, making a potentially good target market. In the future, most acquisitions, joint ventures, and research and development (R&D) labs will take place in this region. The majority of acquisitions will likely be led by corporations with roots in the mature bone and joint health market of the United States and Europe.



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Intellectual Property Trends in Joint Health/Inflammation Products

by Andreas Baltatzis and Gideon Eckhouse

INSIDER's Take

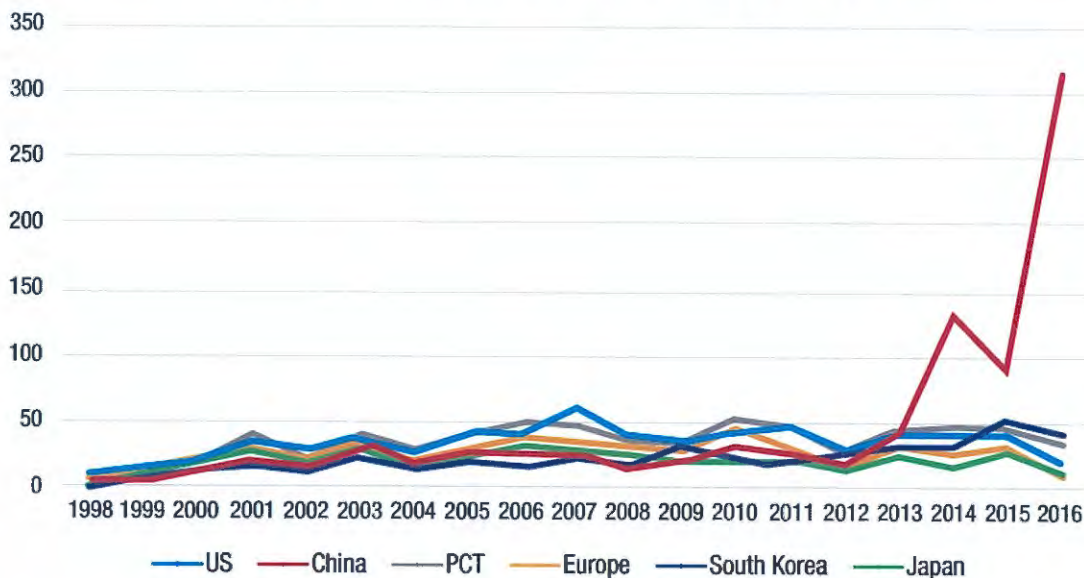
- Patent application filings for joint health products remained relatively consistent over the past 20 years.
- A country-based analysis indicated a very large increase in patent filings for joint health products in China.
- The most common term used for joint health trademarks is simply the word "joint."

Joint health and inflammation continues to be an important market for nutritional products. In particular, joint health is crucial to maintain a level of activity conducive to overall health for both humans and companion animals. Additionally, joint inflammation can be a source of severe pain and disability. Fortunately, a number of naturally derived active ingredients and follow-on compounds have been identified for their use in reducing inflammation and maintaining joint health.



An article from **INSIDER's** 2017 "[Joint Health: Innovating in a Mature Market](#)" Digital Magazine found the level of patent application filings remained relatively consistent over the past 20 years. For an updated survey, the search criteria and definitions were expanded to obtain a larger sample size. The larger sample size also indicated the same stable filing numbers over the past 20 years. However, a country-based analysis indicated a large increase in patent filings in China. This increase corresponds to a National Patent Development Strategy that provided government incentives to bolster the number of domestically filed patent applications. The program resulted in double-digit growth in annual patent filings, as China moves to become an innovation powerhouse.

Patent Applications per Year by Country, 1998 to 2016



IN THIS ISSUE

Business **p.29**

Takeaways **p.40**

Table of Contents **p.2**

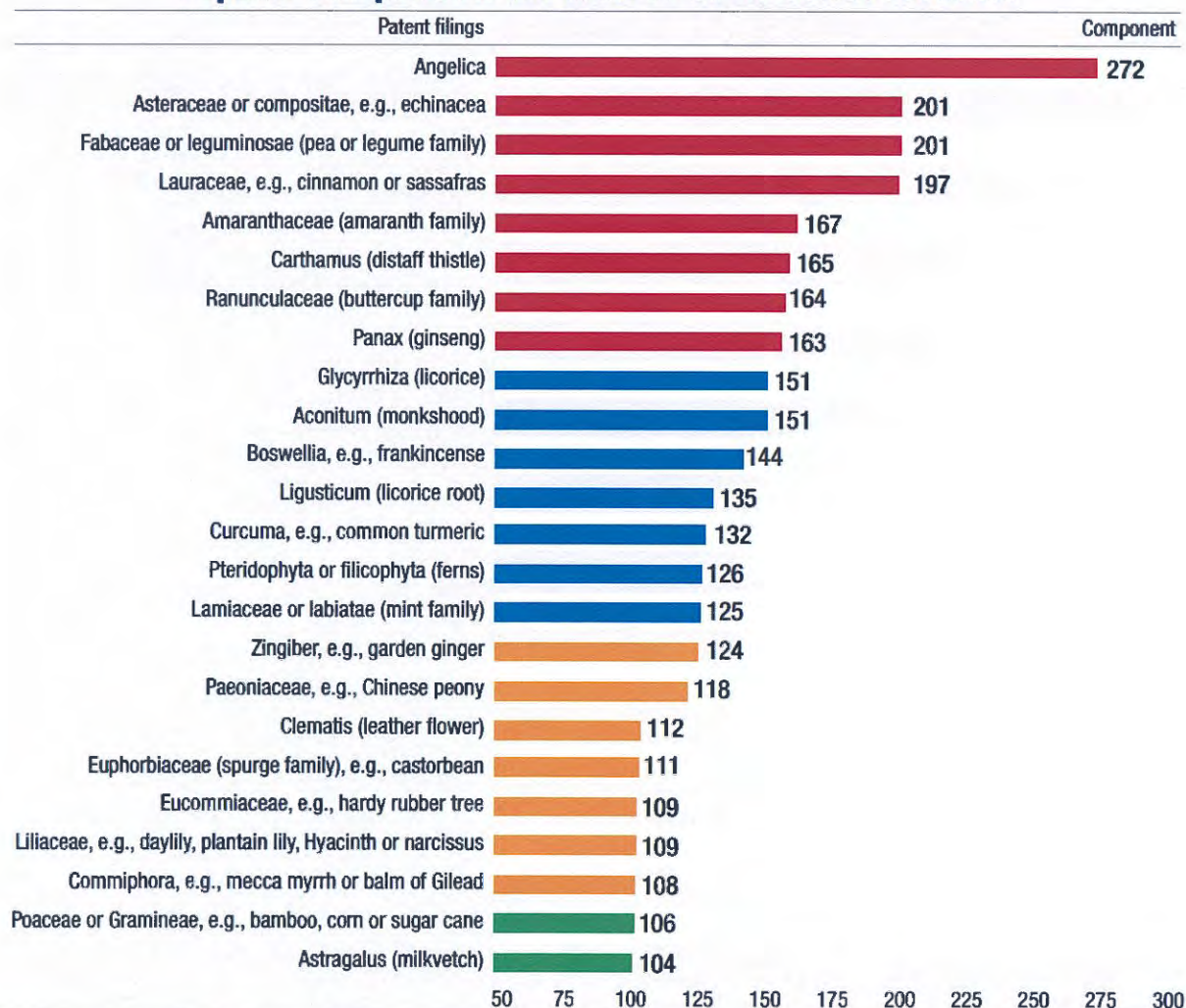
Intellectual Property

The data include Patent Cooperation Treaty (PCT) patent applications, which allow an innovator to file one application with the option of choosing individual patent office filings at the end of 30-month pendency. Additionally, patent filings in the United States continue to decrease, as recent guidance regarding the patent eligibility of naturally derived products has negatively impacted the likelihood of obtaining patents on new innovations.

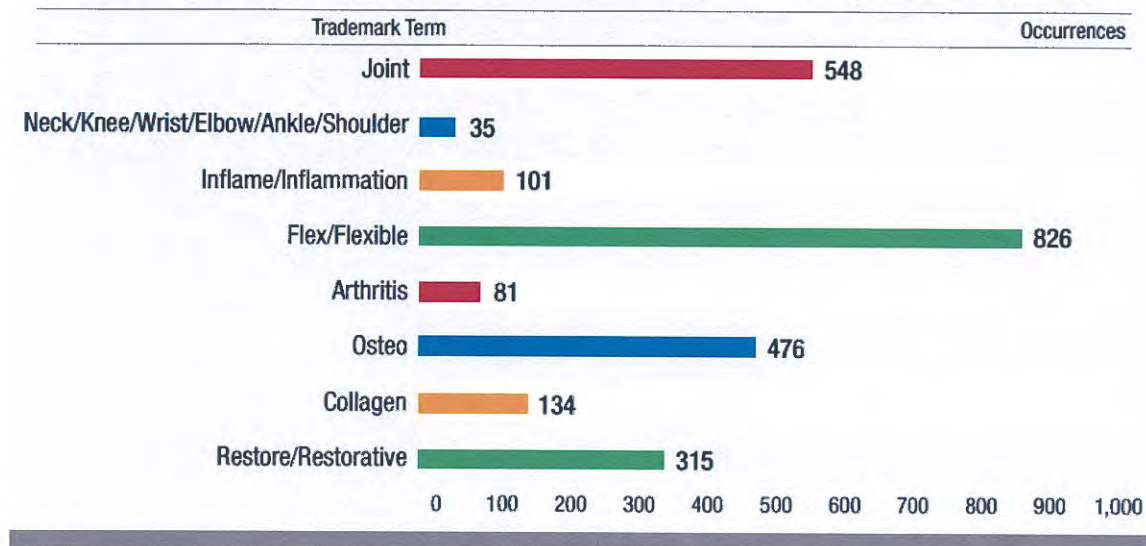
The specific active ingredients incorporated into patented products fit into patent classifications, and may indicate a primary component of a combination product or a starting material for a derivative compound. Naturally derived components alone in their natural state are not eligible for patenting and must be modified either by combination with other ingredients, or by significant modification of the natural ingredient. Alternatively, new methods of use for previously known products may be patentable.

Trademarks are a valuable way of conveying to customers information about a nutritional product. All trademarks have two essential components: the terms used in the mark itself and the goods that limit the scope of trademark protection.

Popular Components in Patented Joint Health Products



Common Terms in Joint Support Nutritional Product Trademarks



The data show that “flex” or “flexible” and other variations are the most common terms used. However, these terms have a scope beyond joint health. The scope of another popular term, “osteo,” includes bone health products, and not just joint health. Therefore, the most common term used for joint health trademarks is simply the word “joint.”

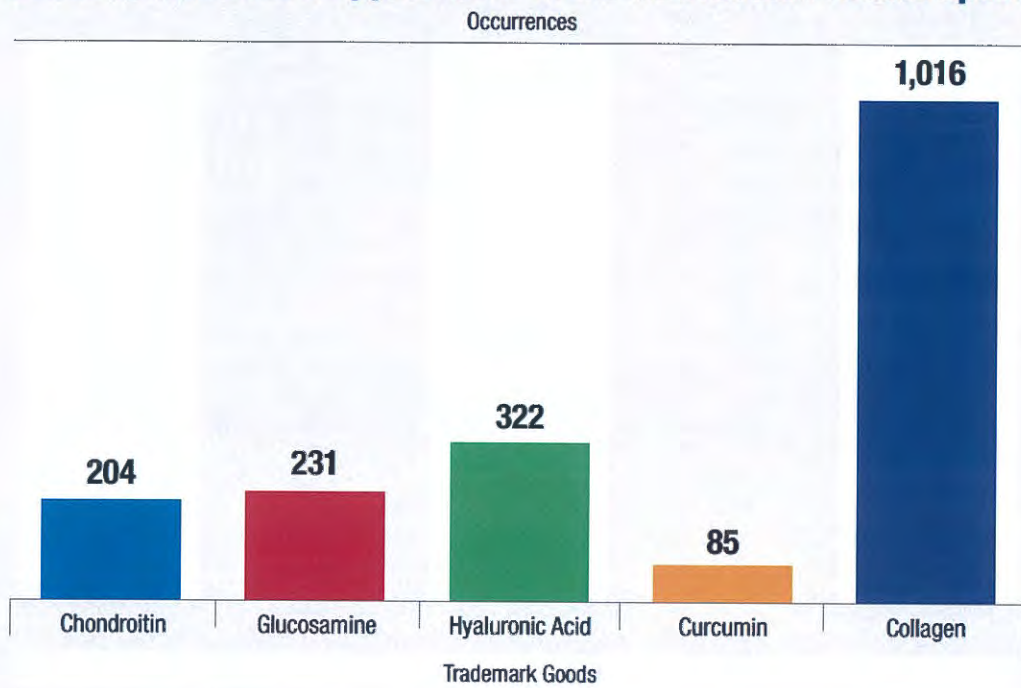
However, a trademark holder cannot obtain rights for such a simple term as “joint” without additional modifiers. This is because trademark law prohibits one person or company from owning the rights to generic terms, i.e., terms that are the name for the product itself. In this case, “joint” is generic for a product implicated in joint health. Therefore, new and creative combinations of terms with “joint” are necessary in order to obtain trademark registration. These terms can include common words such as “strong” or “rescue,” a surname such as “Verebry” or a coined term such as “senaxs.” Each of these combinations have been used to successfully register a joint health product.


The second aspect of a trademark registration, the goods, is necessary to show that the mark is in use with a particular type of product. The U.S. Patent and Trademark Office (USPTO) requires every applicant to provide evidence that the mark is used with a product before granting registration.

The most common term used for joint health trademarks is simply the word “joint.”



Goods in Trademark Applications in the Nutritional Product Space



The goods help define the scope of rights of a trademark registration. In particular, a trademark registration that lists glucosamine in the goods might be limited to products that include glucosamine. The data above show collagen is most commonly used in the goods compared to other goods searched. However, limiting to particular ingredients might not be the best strategy in most cases. The broadest, and arguably most valuable, trademarks might simply list “dietary and nutritional supplements” as the goods. Such a description would not restrict the mark to products containing specific ingredients and could be used to ensnare infringing uses of the mark with a variety of products. 



Attorney Andreas Baltatzis is a director at [KramerAmado PC](http://KramerAmado.PC) (krameramado.com), a boutique law firm specializing in intellectual property (IP). He represents a number of innovative nutritional supplement and nutraceutical companies that improve people's lives every day. Baltatzis also helps companies prepare and implement IP strategies by obtaining patents and trademarks that protect their innovations and cash flow, as well as advising clients on successfully launching new products and brands.



Gideon Eckhouse is a senior associate at KramerAmado, with more than 10 years of experience in patents and trademarks. He assists innovative nutritional supplement and nutraceutical companies in protecting their IP throughout the world. Eckhouse counsels and implements global trademark strategies for new brand launches. Additionally, he prepares and prosecutes patent portfolios protecting new products coming to market.

Joint Health: Steadily, Flexibly Forward

by Steve Myers

As the global joint health market grows a steady 7 percent over the next three years, the category's staple dietary ingredients and products are giving way to a fresh wave of botanicals and specialty compounds, bringing researched joint and inflammation management to a wider, active audience than those with aging bodies.

Beyond Relief. "Consumers want products that improve their health, not products that mask their symptoms," explained Tim Hammond, Bergstrom Nutrition. In fact, as joint health and function is something consumers want to preserve over a lifetime, they are looking for customized joint health solutions that are safe for long-term use. For many, this means a small, daily supplement dose—but for others, including the younger generations, alternative delivery formats are the way to joint regimen compliance.

Herbs on the Rise. Persistent local inflammation is a recognized key driver of wear and tear joint problems, including osteoarthritis (OA). Inflammation is typically a short-term consequence of activities, but chronic or persistent inflammation can have a lasting damaging effect on joints. Turmeric has reached superfood status and is on the rise in joint health, owing largely to its primary anti-inflammatory constituent curcumin. Additional botanical ingredients offering anti-inflammatory and other joint-related researched benefits include ashwagandha, ginger, *Boswellia serrata*, *Terminalia chebula*, *Bacopa monnieri* and *Kaempferia galangal*, which has the cool nickname of "resurrection lily."

Animals to the Rescue. Despite the growing use of botanicals for inflammation and oxidative stress control, joint health still relies heavily on supplying naturally occurring compounds found in cartilage and synovial fluid, which are commonly derived from animal sources. A popular trademark in this category involves collagen, a critical cartilage component. Research has shown undenatured collagen from chicken and collagen peptide ingredients derived from animal skin and bones deliver key amino acids crucial to improving the structure and function of cartilage and connective tissues, including inflammation management. Also, glucosaminoglycans (GAGs) and other compounds found in healthy cartilage are commonly supplemented through popular ingredients like glucosamine and chondroitin from shellfish, but eggshell membrane has emerged as an alternative animal source that also delivers keratin and collagen, as well as anti-inflammatory compounds.

With consumers of all ages, activity levels and lifestyle goals tuning into natural joint health, companies will realize joint health cannot be successfully delivered widely in one formula, one format. Companies may choose to offer personalized solutions or simply have a range of joint-related products consumers can choose from.

Offering glucosamine, chondroitin, methylsulfonylmethane (MSM) and hyaluronic acid (HA) will no longer be enough to stand out in this market. With an array of botanicals offering researched anti-inflammatory and other joint benefits—and innovatively branded, as well as new alternative sources of compounds found in joint structures like cartilage and synovial fluid—joint health formulas will need to push the boundaries to be more unique and comprehensive.

IN THIS ISSUE

Intellectual Property **p.34**

Market Trends **p.42**

Table of Contents **p.2**

