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Support structure

Ingredients for bone and joint health

Vitafoods™ INSIGHTS

CONTENT

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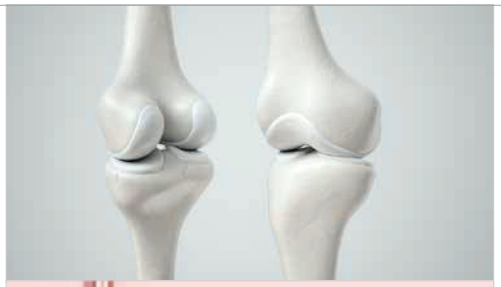

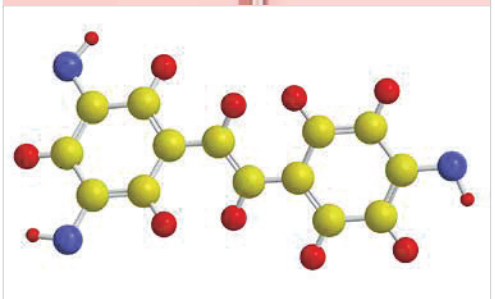

Down to the bone

Since childhood, I've participated in a high-impact sport and never gave too much thought as to how it might be affecting my body. I started experiencing back and neck aches in my late teens—which I chose to ignore. At the age of 21, the pain escalated to the point where I sought medical advice and I was alarmed to discover seven degenerated discs (almost completely dissolved) with several more showing signs of deterioration. It wasn't until then that I decided to get a lot more serious about my bone and joint health. The lesson learnt? Our bodies go through wear and tear more than we realise and it's not wise to think you're immune just because you're young. The levels of activity and strain may escalate the rate of degeneration but, ultimately, our bones and joints will naturally deteriorate as we age. It's never too early to put maintenance in place, and hopefully prevent the early onset of conditions such as osteoarthritis—a condition estimated to affect more than 40 million people across Europe.

Globally, people of all ages are making the effort to adopt healthier and more active lifestyles; consequently, we can expect to see consumers of all ages seek products that support healthy joints and promote comfortable mobility. Coupled with a desire for personalised solutions and alternative delivery forms, the bone and joint health market welcomes companies that offer differentiation from conventional treatment and remedies. Ginger Schlueter provides an overview of ingredient offerings, recent trials and studies, and emerging entries to the market (page 4).

Johannes Haerle walks us through new learnings from the largest clinical study of resveratrol in postmenopausal women, which set out to confirm the earlier evidence of mood and cognitive benefits of low dose resveratrol supplementation in the ageing female population, who are at heightened risk of chronic diseases such as sarcopenia, bone health and dementia.

To wrap up this edition, Shane Heffernan, who will be speaking at Vitafoods Europe 2019, investigates nutraceutical treatment for osteoarthritis. Read more on page 13 on the growing evidence supporting the positive effects of a variety of compounds—namely terrestrial botanicals, marine fauna, and marine botanicals.

The future is bright for natural products that support bone and joint health care, and at the same time offer the market innovation and differentiation.

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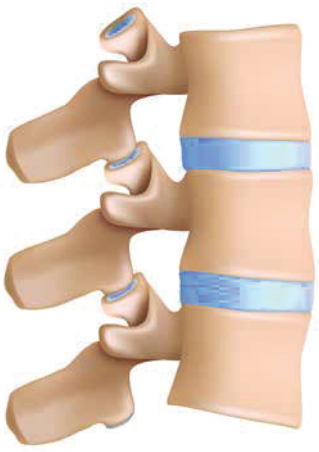

Joint health ingredients

Keeping every body mobile

by Ginger Schlueter

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

Globally, the United Nations (UN) estimates by 2030, older persons (aged 60 and over) are expected to outnumber children under 10 (1.41 billion versus 1.35 billion). In fact, by 2050, UN projects there will be more adults over age 60 than adolescents and youth ages 10-24.

In addition, the world is moving at a faster pace as people of all ages are adopting more active lifestyles, increasing the desire for healthy joints to sustain mobility.

Osteoarthritis (OA), the most common type of arthritis, is estimated by the World Health Organisation (WHO) to affect more than 40 million people across Europe. Joint health supplements are for everyone, no matter their age, and the market for joint health ingredients is steadily growing. 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.

Joint health consumer trends

For companies looking to get their share of the joint health market, identifying the right ingredient or combination thereof is key, along with meeting additional consumer preferences. In general, consumers are seeking more custom formulations for joint health with ingredients shown safe for long-term usage, according to Nena Dockery, technical services manager, Stratum Nutrition. Playing into this is a proactive, preventive, custom approach to joint health.

Appealing specifically to older consumers is a small, once-daily dose along with ingredients boasting well-documented, broad-spectrum safety profiles verified by extensive toxicology testing and ingredient efficacy, and backed by robust clinical trials, explained Juliana Erickson, senior marketing manager, Lonza Consumer Health & Nutrition

Consumers are also 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.

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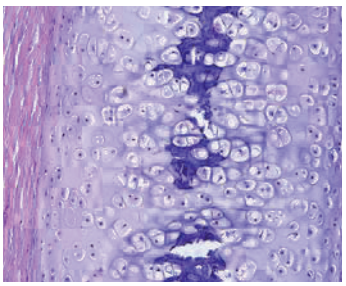
Joint health ingredients

For the body to move freely in multiple directions, synovial joints must be healthy, as these joints "provide the mechanism through which smooth movement can occur between bones," Dockery explained.

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 Oliver Wolf, head of B2B marketing, global, GELITA, high pressure and mechanical strain can break down cartilage, causing pain and joint mobility issues. 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.

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, protect joints and reduce discomfort,[1] support bone health[2] and promote muscle mass.[3]



"The decline in oestrogen production at menopause heightens a woman's risk of osteoporosis

Research showed bioactive collagen peptides (BCP as FORTIGEL®, from GELITA) were absorbed intestinally and accumulated in cartilage, leading researchers to conclude ingestion of BCP stimulates an increase of cartilage tissue metabolism.[4]

In a 2017 study, the use of BCP (as FORTIGEL) was evaluated in reducing pain in athletes with functional knee problems during sport. For the study, subjects ingested 5 g/d of BCPs or placebo for 12 weeks.[5] Pain intensity during activity was evaluated using a visual analogue scale (VAS), with supplementation resulting in statistically significant improvements in activity-related pain intensity compared to the placebo group.

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 experienced 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 hydrolysed (broken down in water) type I collagen (hCol1) has been reported to reduce pain in human osteoarthritis (OA) and support positive influence on chondrocyte function. Male mice with early- to mid-stages of OA degeneration were given either a high dose (38 mg) or low dose (3.8 mg) of bovine hCol1 (as Peptan) each morning for

16 weeks.[7] Researchers drew blood at various intervals to ensure absorption of hCol1; after the study concluded, results 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 II 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 II collagen (as UC-II, from Lonza) helps 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.

Rousselot's Peptan® IIm, a collagen type II matrix, was developed to promote multiple joint health benefits. The ingredient contains a matrix of hydrolysed type II collagen peptides and glycosaminoglycans (GAGs), which mimics the body's natural composition of the cartilage matrix.

In an 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 was shown to help prevent joint problems by minimising local inflammation, protecting the cartilage from degeneration and stimulating chondrocytes to produce lubricating matrix.

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

A 30-day, randomised, controlled trial of 15 subjects receiving 1,500 mg/d KollaGen II-xs demonstrated efficacy by improving essential symptoms in individuals suffering from joint diseases.[11]

Joining the market

A few other popular ingredients are making strong statements in the joint health market.

Avian eggshells and membranes—commonly disposed of as waste—have a high content of bioactive components that have received increasing attention for joint health applications.[12]

In a 12-week, randomised, double-blind, placebo-controlled crossover study, 22 participants consumed 450 mg/d of hydrolysed water-soluble egg membrane (WSEM as BiovaFlex®, from Biova LLC), resulting in improved joint function.[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.

In an in vivo trial to investigate anti-arthritis activity, NEM was administered at up to 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 randomised, 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. 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 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."[17-21]

NEM functions through controlling the secretion of pro-inflammatory substances, including cytokines and matrix metalloproteinases (MMPs).[22-25]

Another new ingredient (TendoGuard™, from AIDP) combines avian eggshell membrane and sternum cartilage for a comprehensive blend of nutrients. In a single-centre 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, randomised, 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 glucosamine, 1,200 mg chondroitin sulphate and 500 mg saccharumlactis; the 'GCM' group received daily 1,500 mg glucosamine, 1,200 mg chondroitin sulphate and 500 mg MSM (as OptiMSM® by Bergstrom Nutrition); 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 optimised 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.[29-31] Additional studies have also shown MSM inhibits pro-cytokine expression[32] and the activation of nuclear factor kappa B (NF-kB)."[33]

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

Other, lesser-known joint health ingredients are also gaining traction in the market.

Boswellia serrata is an herbal extract traditionally used in India for joint health. 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 randomised, double-blind, placebo-controlled study published in 2018 evaluated 50 participants, ages 50 to 70, with knee OA and a WOMAC score less than or equal to 5.39 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.[36]

Joint health affects many people on different levels; it's important to continue researching natural ingredients to help maintain joint health.

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Resveratrol's impact on bone and joint health

Interim insights of the largest clinical study with resveratrol in postmenopausal women

by Johannes Haerle

Resveratrol has raised attention not only for being a very effective antioxidant but also for exhibiting a number of beneficial functions on cellular and systemic levels.[1]

Resveratrol has been shown to exhibit promising effects in reducing oxidative stress and inflammation in cartilage.[2] Its ability to neutralise reactive oxygen species and downregulate a response of inflammation are not the only positive effects shown in this trial. It was also observed that resveratrol promotes osteogenic differentiation of stem cells and potentially triggers bone formation. These outcomes have motivated researchers to further study resveratrol's impact on human bone and joint health.[3]

Clinical study results

In 2014, two clinical studies exploring the effects of resveratrol on bone health were started with Veri-te™ resveratrol utilised in both studies. Findings showed a promising impact on bone health. First, the positive influence of resveratrol on bone metabolism and ability to possibly preserve bone integrity denoted by a primary anabolic modality was confirmed by increased plasma levels of bone-specific alkaline phosphatase (BAP).[4] The results showed that the plasma levels of BAP, a biomarker for bone formation, increased significantly in the resveratrol group vs. placebo. The second study affirmed an increase in the volumetric bone mineral density (BMD) with resveratrol supplementation.[5]

With an oral intake of 75 mg resveratrol twice a day, research indicates the potential reduction of chronic pain in age-related osteoarthritis with resveratrol treatment.[6] In terms of safety and efficacy, another clinical study showed that resveratrol supplementation with meloxicam is superior to meloxicam alone for the treatment of pain and improvement of physical function in patients with knee osteoarthritis.[7]

As the decline in oestrogen production at menopause heightens a woman's risk of osteoporosis,[8] postmenopausal women have been identified as a vulnerable population who may also benefit from resveratrol supplementation, a strategy that can be easily incorporated into the daily diet.[9]

Daily supplementation with resveratrol offers women a convenient, science-backed approach for managing menopause-related symptoms and counteracting accelerated physical decline and the loss of BMD caused by menopause.

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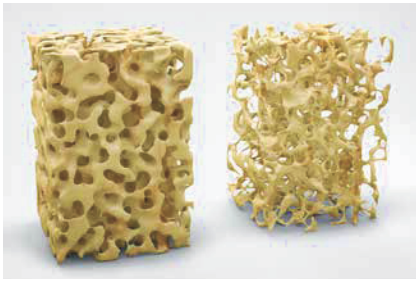
It is recommended that post-menopausal women and men 50 and older obtain an x-ray measurement to quantify bone density on a regular basis, especially if they have recently broken a bone. This enables the diagnosis of osteoporosis and prevention before a broken bone occurs. Measured as a 'T-score', the bone density test refers to the bone density of a healthy 30-year old adult. The lower a person's T-score, the lower the bone density or the higher the risk of a bone fracture.



"The decline in oestrogen production at menopause heightens a woman's risk of osteoporosis.

RESHAW trial

RESHAW (Resveratrol Supporting Healthy Ageing in Women) is the largest (140 participants) and longest (two-year) randomised crossover trial of supplementation with resveratrol (as Veri-te) in postmenopausal women between the ages of 45 and 85 years old. It was designed to confirm the earlier evidence of mood and cognitive benefits of low dose resveratrol supplementation in this population who are at heightened risk of chronic diseases including sarcopenia, bone health and dementia.[10]The benefits of resveratrol may be mainly attributed to improvement of the vascular function mediated by both estrogen receptors and SIRT1 activation, and this could have a favourable effect on osteoporosis as suggested by a rat osteoporosis model.[11] an agonist of SIRT1, could have favorable effect on osteoporosis and to explore the underlying mechanisms. Rat osteoporosis model (ovariectomy group, OVX

The RESHAW interim evaluation after 12 months revealed significant benefits of resveratrol treatment vs a placebo. BMD measured in the lumbar spine increased by 1.5 percent, equating to an 18 percent improvement in T-score. In particular, resveratrol tended to reduce the loss of BMD in the neck of the femur, resulting in a 12 percent improvement in FRAX T-score (a Fracture Risk Assessment tool), a 36 percent reduction in hip fracture risk and a 9 percent reduction in the 10-year risk of a major osteoporotic fracture. Although supplementation did not improve lean muscle mass, the hand grip strength of the recruited post-menoapausal women tended to increase by 2.9 percent.

Takeaways

These interim data demonstrate the potential benefits of resveratrol supplementation for postmenopausal women at heightened risk of osteoporotic fractures. Having reached the half-time of the clinical trial, it can be expected that these promising results will be strengthened by individual comparisons at the end of the 24-month study. It is encouraging that supplementation tended to increase hand grip strength and had a beneficial effect on sarcopenia that correlates well with the observed improved bone health. Lastly, resveratrol's impact on potential reduction of chronic pain in age-related osteoarthritis is very promising. Further biomarkers and test results currently under evaluation will shed more light into the very promising features of resveratrol.

Johannes Haerle, PhD, MBA, senior technical manager at Evolva SA has an M.Sc in Biochemistry. He received his PhD in Pharmaceutical Sciences, after which he performed a postdoctoral Marie Curie research fellowship at the Department of Biosystems Science and Engineering, ETH Zurich. In 2018, he received an MBA degree from the Faculty of Business, Economics and Informatics from the University of Zurich. Haerle spent 15 years working in different laboratories and gained experience in biochemistry, and biotechnology using plant, mammalian, bacteria and yeast originated cellular systems. By combining his knowledge in science and his business acumen, Johannes provides technical advice and support regarding clinical and other scientific evidence to foster a better understanding of Evolva's health ingredients portfolio both internally and externally.

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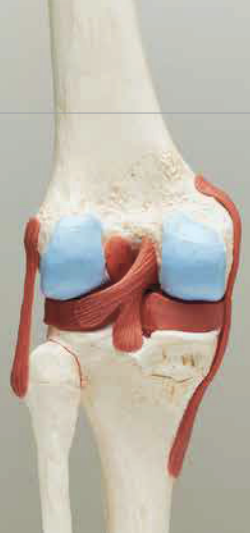
Targeting OA the nutraceutical way



NSAIDs and analgesics for treatment of osteoarthritis

by Shane M Heffernan

Chronic pain is a considerable health concern worldwide—affecting almost 30% of all European adults. Those who suffer from chronic pain certainty know the social, economic and health burden—not to mention the potential issues that are not immediately noticeable such as immune dysfunction, cardiovascular problems (related to the stress response), and respiratory illness.[1] Osteoarthritis (OA) is one of the most common causes of chronic pain and the most common cause of joint pain.[2] OA is a progressive pro-inflammatory condition of synovial joints that affects approximately 13% of the over-50 population—with 16 to 27% of those reporting knee joint OA—that has no real cure.[3-7]

Conventional offerings

There are two main pharmacological options for chronic pain management: non-steroidal anti-inflammatory drugs (NSAIDs, particular enzyme inhibiters), and opiate/opioid analgesics. NSAIDs are the most widely used medications because of the lower potential for addiction—as shown by the U.S. opioid epidemic.[8] The prevalence of 'non-aspirin' NSAID use has been well studied and is dynamic across age, body mass index (BMI) and geographical ancestry—ranging between 15 and 45%, with women being the greatest users and ibuprofen generally being the most reported.[9-11] These NSAIDs are the traditional approach for early clinical management of mild-to-moderate OA and in the United States 65% of all OA patients are prescribed NSAIDs for pain management, which is the current recommended strategy for OA clinical management by leading authorities.[12] While some NSAIDs are effective at improving pain and physical function, they come with some significant and potentially harmful side effects such as gastrointestinal complications, renal disturbances and severe cardiovascular events[13]—although some of these risks may be reduced using topical administration such as diclofenac gel/cream.[14-15]

Complications and questions

Two recent large-scale studies have shown that, depending on the particular medication, the risk of hospital admissions (due to heart failure) can be nearly two times greater[16] and in OA/rheumatoid arthritis (n=24,081) ibuprofen (generally speaking, the most used NSAID) had the highest rates of NSAID toxicity.[17] It is important to note that other pain medications are often used by patients with

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OA; for example, roughly 34% use Paracetamol,[18] in isolation or in combination with NSAIDs. In fact, the effectiveness of Paracetamol to improve pain management has recently been called into question,[19] shown to be ineffective for treating OA pain[20-21] and may have similar side effects as ibuprofen,[22] particularly when consumed at higher doses.[23]

Given the possible side-effects, any reduction in NSAID and analgesia use (and the resulting potentially harmful side effects) is of particular importance to public health. As such, several non-pharmaceutical alternatives have been developed that may reduce NSAID and analgesia use while maintaining pain reduction and improvements in physical function. This mini-review will discuss those nutraceuticals that are currently not in mainstream use but may have the potential to aid in treatment of OA (like the well discussed glucosamine and chondroitin, which will not feature in this article). These nutraceuticals can be divided into three categories defined by their origin and are presented in Table 1 (page 19):

- Terrestrial Botanicals—compounds derived from 'land' plant sources (avocado/soybean, pine bark extract and turmeric/curcumin)
- Marine Fauna—derived from marine animals (fish oil and green lipped mussel)
- Marine Botanicals—compounds derived from 'marine' plant sources (*Lithothamnion corallioide*)

Terrestrial Botanicals

Turmeric/curcumin extracts (spices mainly used in South Asian cooking) have the most evidence for improving OA symptoms, with some recent data on NSAID and analgesics use.[24] Two studies have even directly compared turmeric/curcumin extracts to NSAIDs.[25-26] Put to the test against oral ibuprofen or diclofenac (commonly used NSAIDs), turmeric/curcumin extracts improved knee OA (KOA) pain, physical function, pain during stair walking, inflammatory biomarkers, and resulted in less side effects.[25-27] But how do turmeric/curcumin extracts fare at reducing NSAID and analgesic use on OA patients?

Patented formulations of turmeric/curcumin extracts have been developed around the world and have shown some positive effects. For example, in European KOA patients, the addition of a proprietary combination (as Indena's Meriva®: curcuminoids 20%, phosphatidylcholine 40%, and microcrystalline cellulose 40%) to the 'best available treatment', reduced NSAID and analgesia use by 63% compared to the control group ('best available treatment' only). This reduction resulted in the fewer side effects between 45 and 67%, depending on the specific adverse advent, compared to control group (2 to 12%).[28] Similarly, an alternative proprietary combination (as Sabinsa's Curcumin C3 Complex®: curcuminoids 500 mg capsules with 5 mg Bioperine®) reduced the use of naproxen by 84% (compared to 19% in placebo) in Iranian KOA patients. A further alternative (as Theravalues' Theracurmin®) reduced dependence in Japanese KOA patients on celecoxib (from 70% to 30% versus 80 to 60% in placebo). This data clearly point to the positive impact that turmeric/curcumin extracts can have on NSAID and analgesia use in the short term (study durations were generally less than 12 weeks) but long-term effects are still speculative.

Nonetheless, alternative terrestrial botanicals have shown some additional advantages for OA. Two studies have investigated avocado/soybean extracts and their potential for NSAID and analgesics use.

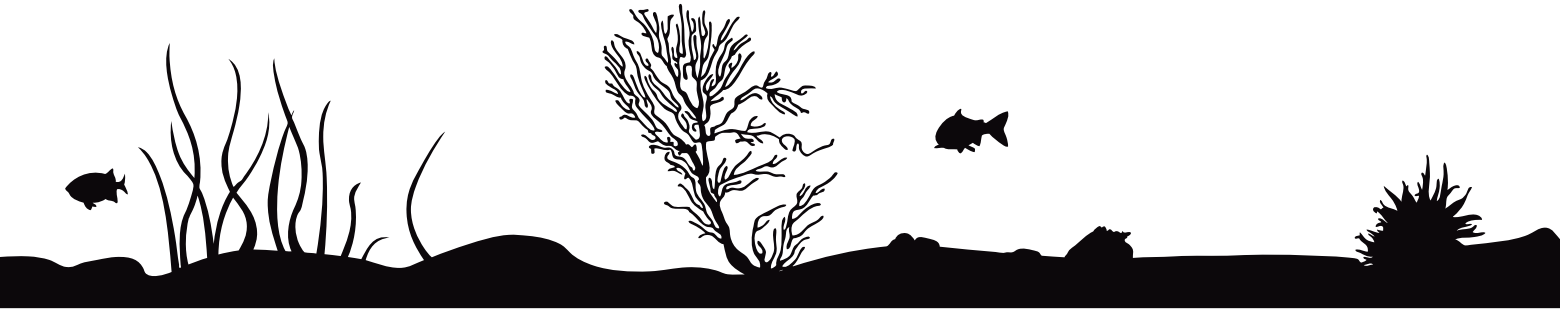
One large randomised control trial (n=260) showed that after 30 days of supplementation the extracts reduced daily intake of NSAID and analgesics compared to placebo and that 71% (compared to 36% in placebo) of avocado and soybean extract participants reduced their daily intake by 50%.[29] This was somewhat supported by a small (n=31) observational study showing that the proportion of OA patients using analgesics and NSAIDs dropped by 34% over six months consuming avocado/soybean extracts.[30] Although in the large scale 'real-world' (PEGASus) study cohort where analgesic and NSAID use was assessed by phone interview bi-monthly over two years, avocado and soybean extracts showed no effect on reducing medication use.[31] So, it is safe to say that there is still some debate over avocado and soybean extracts to alleviate analgesics and NSAID use.

Finally, as study using patented pine bark extract (as Pycnogenol®, from Horphag) reduced NSAID use by 58% over 12 weeks compared to only 1% in the placebo group. Furthermore, this resulted in reduced hospital admissions and days spent in hospital by 50% compared to placebo, in early stage KOA(n=156).[32] Again, these data are interesting but require further replication.

Marine Fauna

New Zealand Green Lipped Mussel (GLM: *Perna canaliculus*) lipid extracts have been investigated for their potential benefits for OA symptoms. Moderate-to-severe hip and knee OA patients received 600 mg of Biolex®-GLM for 12 weeks or a placebo and were allowed to consume paracetamol for additional pain relief.[33] Participants consuming the placebo took more paracetamol each week of the 12 weeks; however, they did not differ in NSAID equivalence score. This suggests that there may be some potential for GLM to reduce analgesic medication but maybe not when patients feel that stronger mediation is needed.

Fish oils have also shown some promise to reduce medication use in OA. A proprietary combination of omega-3 and omega-6 fatty acids, *Urtica dioica* (common nettle), zinc and vitamin E (Phytalgic® from Phytea) progressively reduced NSAID and analgesia use over a three-month period (6.5 Paracetamol 500 mg-equivalent per week, compared to 16.5 in the placebo group, n=81).



Marine Botanicals

The marine red algae species *Lithothamnion corallioide* rich in sea-derived minerals, including calcium and magnesium (as Marigot's AquaminF®), have recently been investigated for a potential impact on NSAID usage. In a randomised control trial of moderate-to-severe KOA patients, AquaminF® was an effective agent to improve physical performance (six minute walking distance) when NSAID use was intentionally reduced by approximately 50%, but not when reduced to zero medication.[34] This suggested there may be some potential for AquaminF® to reduce the KOA-related drug dependency, however as with all of the previously mention nutraceuticals possibly more effective in combination with others.

Conclusion

This data is of considerable interest to those suffering from OA and health care providers concerned with the broader health of OA patients. There appears to be a growing body of evidence suggesting that a variety of nutraceutical compounds in preparatory formulations could provide some relief from the burden of NSAID and analgesic dependence and the associated short-term side effects. However, currently the data is limited with respect to replication and duration making long term conclusions.

The one exception is turmeric/curcumin extracts that in a recent meta-analysis showed to be effective in improving OA symptoms (and may even be better than NSAID)—but the authors still call for significantly more research. Nonetheless, the potential for combinations of nutraceuticals that may have further additive effects on NSAID and analgesic reduction have rarely been investigated, but has been recently recommended.[35]

To this end, my team and I at University College Dublin, Ireland have just completed a randomised control 'crossover' trial investigating the combination of *Lithothamnion corallioides* with additional magnesium and pine bark extract on NSAID and analgesia use (among other variables) compared to the market leader glucosamine sulphate. This preliminary pilot data have shown some promising results and are currently under preparation for peer-review publication and will be presented at Vitafoods Europe 2019. The future is bright for nutraceutical products, but there is still work to be done!

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Table 1

Original source	Treatment regime	Effect on OA analgesia and NSAID	Reference
Avocado/soybean unsaponifiables (ASU)	Avocado/soybean unsaponifiables 300 mg or 600 mg ASU for three months	↓ NSAIDs and analgesics intake by more than 50% in 71% of patients receiving 300 mg or 600 mg, compared to 36% of patients receiving placebo.	(Appelboom, Schuermans, Verbruggen, Henrotin, & Reginster, 2001)
Avocado/soybean unsaponifiables	Piascledine/ASU (300 mg daily) for six months	↓ Proportion using analgesics and NSAIDs from 58.8% to 24.9% (p=0.001).	(Gluszko & Stasiek, 2016)
Fish oil	Phytalgic (fish-oil, vitamin E, Urtica dioica) three capsules daily for three months	↓ NSAIDs use (0.4 defined daily dose/day) vs the placebo arm (1.0 defined daily dose/day), (p=0.02) ↓ Analgesic use (6.5 paracetamol-equivalent tablets/week) vs the placebo arm (16.5), (p=0.001),	(Jacquet et al., 2009)
Green lipped mussel	600 mg of BioLex(R)-GLM extract daily or placebo for 12 weeks	↓ Paracetamol use (p=0.001) compared to placebo	(Stebbings, Gray, Schneiders, & Sansom, 2017)
Pine bark extract	Pycnogenol (pine bark extract) 100 mg for three months	↓ Use of drugs by 58% (p=0.05) versus 1% under placebo ↓ Gastrointestinal complications by 63% compared to 3% under placebo	(G. Belcaro et al., 2008)
Turmeric	Turmeric extracts (2 g of C. domestica extracts/day) or ibuprofen (800 mg) for zero, two, four and six weeks	↓ Pain on walking stairs (p=0.016) compared to ibuprofen, No significant difference from ibuprofen in pain on level walking and time spent during 100 m walk and going up and down a flight of stairs	(Kuptniratsaikul, Thanakhumtorn, Chinswangwatanakul, Wattanamongkonsil, & Thamlikitkul, 2009)
Turmeric	Turmeric extracts (1,500 mg of C. domestica extracts/day) or Ibuprofen (1,200 mg/day) for four weeks	↓ WOMAC final sub-scores (total, pain and function) compared to initial scores at all time points, and was non-inferior to ibuprofen (p=0.010, p=0.018, and p=0.010 respectively) ↓ Rate of abdominal pain/distention compared to ibuprofen (10.8% vs 18.1%, p=0.046)	(Kuptniratsaikul et al., 2014)
Curcumin	Meriva tablets, a curcumin-phosphatidylcholine phytosome complex, 200 mg equivalent curcumin daily with best available care (BCA) compared to BCA only as control for eight months	↓ Use of NSAIDs (63% reduction compared to 12% in control) ↓ Gastrointestinal complaints (38% reduction compared to 15% in control)	(Gianni Belcaro et al., 2010)
Curcumin	Theracurmin (180 mg of curcumin) for 8 weeks	↓ NSAID (celecoxib) dependence (p=0.0252)	(Nakagawa et al., 2014)
Curcumin	C3 complex, 500 mg curcuminoid capsules including 5 mg Bioperine, Three times daily for six weeks	↓ Proportion of subjects using naproxen (84% in curcuminoids group and 19% in placebo group, p =0.001)	(Panahi et al., 2014)
Curcumin	Curcumin: 500 mg/capsule twice daily, Curcumin 500 mg + diclofenac sodium 50 mg/ capsule twice daily, diclofenac 50 mg/ capsule twice daily, all for eight weeks	↓ Disease Activity Score (45%), CRP (52%), American College of Rheumatology score, improved pain (60%), erythrocyte sedimentation rate (11%), greater in curcumin	(Chandran & Goel, 2012)
Lithothamnion corallioides (red algae)	AquaminF, 267 mg Aquamin, 3 capsules per day, three times a day for 12 weeks	↑ ROM (difference, 5.2° ± 2.2, p=0.028) and 6MWD (difference, 136 ± 57 ft, p=0.03) following 50% forced reduction from all NSAID in AquaminF compared to placebo No difference in rescue medication (acetaminophen) consumption between groups	Frestedt (Frestedt, Kuskowski, & Zenk, 2009) et al., 2009

Partially adapted from Wang et al., 2018 (Wang, Leong, Cardoso, & Sun, 2018)

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Takeaways for Your Business

With a vast population of active individuals of all ages and the elderly living longer, the bone and joint health market is no longer looking to solely target the ageing population. Established companies are looking to differentiate their offerings and new entries to the market will succeed by identifying new ingredient combinations and meeting consumer demands for personalised solutions and alternative formulations.

Osteoarthritis remains the most common form of arthritis and consumers will continue to seek out products that protect their bones and joints over the long-haul. Natural ingredients and extracts are proving themselves effective in managing conditions and symptoms pertaining to bone and joint deterioration. A number of completed and ongoing trials are revealing data in favour of nutraceutical solutions, which is of increasing interest to both consumers and companies looking to tackle broader bone and joint health. As our experts identify, eggshell membranes, turmeric, curcumin, green lipped mussel, and red algae are amongst the extracts and ingredients backed by science as prospects for the future market.

Resveratrol is a well-known ingredient for the bone and joint health market, appreciated for its antioxidative and cartilage protection properties. However, half-time results from a recent clinical trial show promising results for specially-developed resveratrol supplementation in postmenopausal women, who are at heightened risk of osteoporosis and bone fractures.

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