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Bone and Joint Health:

Skeleton Support

Vitafoods™ INSIGHTS

CONTENT

March 2018

Keep on Moving

As a teenager, I was very active; I used to love running and hurdling and thought nothing of my joints as I chased PBs and bounded around tracks—until injury struck. Suddenly, my knees were suffering and I learnt the hard way I needed to take better care of my joints. At the same time, I learnt women have a greater prevalence of osteoporosis—a loss of bone mass which predisposes us to fractures. Between 20 and 30 years of age, as I discovered, women reach maximal bone density, a level that must sustain us for the rest of our lifetimes. Now, more than ever for me at least, is the time to pay attention to my bone and joint health.

As Roberto Martinez Mockel explains on page 4, the complexity of the osteoarticular system requires special attention. It provides us with structure, balance and movement, and involves every bone, joint, ligament, tendon and cartilage in the body. Prevention in osteoarticular care is fundamental as it is the most effective tool in approaching osteoarthritis and osteoporosis. Fortunately, there is plenty we can do as the two essential pillars to maintaining good osteoarticular health are a good diet and regular exercise.

Dr Mark Miller offers an interesting perspective to joint health on page 10, as he walks us through the history of managing joint inflammation, detailing the divergence in nutraceutical and pharmaceutical approaches and introducing the Amazon rainforest as a 'botanical pharmacy replete with opportunity' for joint health ingredients. Cat's claw is a vine—the bark of which is made into a tea and consumed for chronic inflammation—offering great potential for joint health care.

Another ingredient playing a significant role in promoting bone and joint health is curcumin. Shaheen Majeed explains well-researched natural products can be safe and effective in addressing bone and joint-related issues and explores the clinical trials supporting curcumin, *Boswellia serrata*, and ginger.

Jim Beakey wraps this edition up with his piece on vitamin K2—the missing ingredient for bone health. He describes the 'bone health triangle', where vitamin K2 constitutes a crucial part of daily supplementation as it facilitates calcium and vitamin D3 in optimally supporting bone health. Importantly, most people are likely to be K2 deficient, with this ingredient applicable to most consumers at all ages.

Bone and joint health are growing concerns around the world, particularly with an ageing population, and inflammatory joint conditions can strike anyone—luckily, a good diet, thoughtful supplementation and regular exercise will stand us all in good stead for supporting our skeletons throughout our lifetimes.

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Understanding the Osteoarticular System

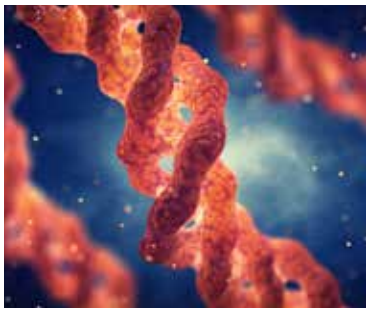
by Roberto Martinez Möckel

Optimal human health requires maintaining balance between the function and structure of the systems that constitute it. Over millions of years, evolution has achieved an almost perfect machinery comprising a set of heterogeneous systems which synchronously, synergistically and efficiently work in order to achieve a a healthy organism. Among all the systems human beings comprise, the osteoarticular system is the structural and functional cornerstone.

The osteoarticular system is continuously renewing. It structurally provides the organism with balance and movement, and in terms of functionality, this system acts as a mineral reservoir.

This system involves different types of elements, bones and soft tissues. Those which represent an essential part of joints—ligaments and cartilage included—are specialised tissues joining structures linked to movement, so they should have characteristics that provide resistance and elasticity—collagen and elastic fibres.

Bones, which provide the structural basis of the organism, are made of calcified tissue formed by inorganic substance, organic substance and specialised cells interdependent with each other. Collagen takes centre stage in the structure of bones, since it is present in 90 percent of the organic matrix, with glucosamine and chondroitin (the proteoglycans) comprising the remaining 10 percent.



Collagen takes centre stage in the structure of bones, since it is present in **90 percent** of the organic matrix, with glucosamine and chondroitin (the proteoglycans) comprising the remaining **10 percent**.

The complexity of the osteoarticular system requires special attention. As life expectancy increases, it becomes important that the global population knows the daily habits to strengthen bone health.

Two essential pillars in our daily life to maintain good osteoarticular health are a good diet and the daily performance of physical activities.

Dietary sources of vitamin K, such as spinach, broccoli and Brussels sprouts, are important aspects, as are sources of vitamin C, including strawberries, oranges, tomatoes and kiwis. Legumes provide magnesium and calcium, while eggs offer sulphur, and whole grains—such as wheat, rice and quinoa—provide silicon and magnesium.

Dried fruit contains polyphenols—with antioxidant properties—which facilitate the renovation of the bone mass and the structure of bones.

Oily fish like tuna, mackerel and sardines have high protein value and are essential to maintaining joints and supporting cartilage synthesis, as well as reducing recovery time after an injury.

Water is also essential—hydration keeps all joint structures lubricated, especially cartilage.

The recommended daily intake values for calcium and vitamin D depend on age. Adults up to 50 years of age should take 1,000 mg of calcium and 200 international units (IU) of vitamin D. Adults over 50 years should take 1,200 mg of calcium and between 400 and 600 IUs of vitamin D.

Enjoying good joint health while maintaining healthy joints and bones requires incorporating a healthy lifestyle by maintaining a balanced weight. The disadvantages generated by being overweight are multiple: it damages joints, promotes inflammatory phenomena and prepares the body for imbalances as severe as those shown in metabolic syndrome X (Type 2 diabetes, cholesterolemia and high blood pressure).

Regular exercise
also **strengthens muscles**
and **ligaments** that are part of joints.

Supplementation in the self-care of the osteoarticular system is essential from around 35 years of age in order to ensure adequate levels of nutrients.

Prevention in osteoarticular care is fundamental. Recently, there has been an exponential increase in knowledge of health-related issues, which offers in depth knowledge of different pathologies and how to treat them in advance, thus increasing quality of life. As a consequence,

life expectancy increases every decade, making pathologies that were previously related to ageing more frequent. This is evidenced through the increase in health care consultations related to osteoarticular pathologies such as osteoarthritis, osteoporosis and arthritis over the last 20 years.

It is necessary to highlight that the profile of patients with osteoarticular pathologies is different in women. Women have a bone structure different from men's, since their bone metabolism depends to a great extent on female sex hormones. Such hormones stimulate the creation and maintenance of bones and have a preventive role in different joint diseases. As child-bearing age ends, the levels of female hormones decrease and the number of osteoarticular diseases increases significantly.

The most effective tool in approaching to osteoporosis is prevention. Osteoporosis appears as a loss of bone mass and therefore a weakening of the bone due to the appearance of pores, which predispose to fractures as a result of minor trauma. Between 20 and 30 years of age, women reach the maximum level of calcium in their bone structures and this amount will be administered for the rest of their lifetime.

Hence the importance of following an adequate diet, exercising regularly, consuming the number of calories adjusted to their height, and of avoiding habits such as alcohol and tobacco.

It has been observed that overweight women have a lower risk of suffering from osteoporosis than thinner women do. During adolescence, it is important to avoid harmful behaviours caused by psychological alterations—such as bulimia and anorexia—since the consequences in bone metabolism at the critical age of structural formation are the development of severe osteoporosis later in life.

During menopause, there is a serious decrease of bone density, which reaches its maximal loss in the first 10 years of this post-fertile period. Studies should be carried out during this period so as to determine the intensity of the loss and restore calcium levels as soon as possible.

Women
have a **bone structure different from men's**, since their bone metabolism depends to a great extent on **female sex hormones**.

It is imperative to detect low levels of calcium by means of blood tests or by conducting studies based on bone densitometry, which is easy to perform and provides a large amount of relevant information to avoid further consequences.

Furthermore, it is important to take into account that osteoporosis does not present symptoms. It is therefore a silent pathology with serious consequences, although it is easily preventable.

Due to its special physiology, women are also the target of another osteoarticular disease: osteoarthritis, suffered by men as well, but with higher prevalence and incidence in women. Osteoarthritis is a degenerative disease of the articular cartilage and the bones it covers. Cartilage wear leads to the fragmentation and even disappearance of cartilage.

This pathology is associated with pain, malformations, joint inflammation, and some stiffness in the affected joint. The most frequently affected areas are knees, the spine (cervical and lumbar), the hips, and hands.

Cartilage wear
leads to the fragmentation
and even disappearance of cartilage.

Osteoarthritis in the hands is very commonly linked to past family history and leads to malformations that can cause hand dysfunction and prevent it from doing common tasks. On the other hand, osteoarthritis in the lumbar spine, hip and knees can be prevented by means of general measures like maintaining an adequate weight, doing exercise regularly and avoiding injuries. There are currently medications that help to improve the symptoms of osteoarthritis and slow down its progression. However, these medications are not exempt from side effects, so it is necessary to take into account the risk/benefit balance and individualise their use for each patient.

The key word in the maintenance of osteoarticular health is prevention; carrying it out from an early age by incorporating healthy life habits, and in annual health checks and bone densitometry studies.

Another aspect related to osteoarticular health is sports practice. Physical inactivity makes muscles weaker and joints less elastic, so activities such as walking, swimming or doing flexibility exercises (yoga) are a great help to keep joints flexible without forgetting that maintaining a good posture guarantees the balance between muscles (agonistic/antagonistic).

Regarding sports, it is important to consider that its practice has unique benefits for general health and specifically for osteoarticular health. There is increasing evidence of the importance of regularly performing physical exercise, but we have to know how to practice it and how often to avoid unwanted collateral effects. It is well known that repetitive exercise has an impact on joints, so the decrease thereof will be a consequence of following the advice of specialised professionals.

Physical exercise must be adapted to the individualised physical conditions of every person. Some disciplines require more work for joints and any exercise should be combined with gentle stretching. If we are interested in practicing less demanding joint exercises, walking an hour per day or yoga should be first choice.

Strength exercises or isometric exercises are interesting to help maintain muscle mass and avoid sarcopenia. The key when practising sport is to set realistic goals, advised by a health professional, since personalised osteoarticular care is the objective to be achieved as a guarantee of constant quality of life.

Apart from a correct diet, healthy physical activities, maintaining an adequate weight and avoiding socially accepted bad habits (alcohol and tobacco), it is essential to include 'quality supplementation', understood as the intake of essential food supplements, such as collagen, vitamin C, minerals, d-glucosamine, chondroitin, or hyaluronic acid inter alia.

These ingredients, in proper proportion and quality, will prevent the reduction of the osteoarticular mass loss, increase mobility and provide a reduction of pain and inflammation. These three factors are the most prevalent in osteoarticular pathologies and cause the greatest number of disabling diseases accompanied by very relevant socioeconomic consequences, reducing life quality significantly.

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Historical Insights to Joint Health

by Dr Mark Miller

Active involvement in inflammation research for 36 years offers the luxury of perspective. However, personal experience pales with traditional medicine—knowledge acquired over thousands of years. This article will describe the merger of those perspectives: those of modern science and the tried-and-trusted traditional approach to joint health management. With reflection, this will document where mergers went smoothly and where, on occasion, we lost our way and dropped gems with our giddy fascination with our new technological toys and their free-flowing fiscal fortitude. During this short historical stroll, my hope is we will better appreciate the remarkable opportunities associated with immense natural resource that is the Amazon Rainforest.

A short walk through the history of managing joint inflammation

Until the late 19th century, pain management was dominated by two botanicals: the less addictive willow bark with its bioactive—salicylate—and the poppy and its derivative opium. This landscape changed dramatically when Dr Hoffman discovered salicylate could be modified with an additional acetyl group, forming acetyl-salicylic acid or aspirin. In the 20th century, a series of 'aspirin-like' compounds were generated and marketed as non-steroidal anti-inflammatory drugs (NSAIDs).

While NSAIDs attenuated the pain and swelling associated with joint pain and arthritis, rheumatologists knew they had no impact on the progression of arthritis. They were dispensed for symptomatic relief, although subjects thought with the reduction in pain and swelling that they were being 'cured'. Physicians rarely set this record straight. Thus, NSAIDs were dispensed liberally and with that expansive distribution we learnt chronic, high dose NSAID consumption comes with a terrible cost—a high mortality and morbidity resulting from compromised renal and gastrointestinal function. The Nobel Prize winning discovery by Sir John Vane— NSAIDs and aspirin work on an enzyme called cyclo-oxygenase (COX)—helped create more potent pharmaceutical offerings. Then an important discovery was made: COX exists in two distinct forms. COX1 is present in tissues at all times, while COX2 is normally absent, but during inflammation the gene for COX2 is expressed and the enzyme generated. In other words, COX2 is only present during inflammation.

This discovery led to the development of the COX2 inhibitors: NSAIDs more selective for COX2 than COX1, including celecoxib (Celebrex) and rofecoxib (Vioxx). Ideally, COX2 selective NSAIDs would have less impact on normal COX activity and only work when there was inflammation, i.e. when COX2 was expressed. Initially, these innovations were well received, reflecting the magnitude of the problems with traditional NSAIDs—deaths from gut damage and kidney failure.

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LESSON 1. **While subjects did indeed have less gut and kidney damage, the differences were not overwhelming.**

Further COX2 inhibitors were associated with a substantially greater risk for heart attack and stroke. This disturbing trend was initially brushed aside but eventually Vioxx was removed from the market for this reason.

All of this reflects the power associated with a pharmaceutical approach to inflammation.

LESSON 2. **NSAIDs, whether they showed specificity for COX 2 or were non-selective, still had no impact on the progression of joint damage in arthritis.**

They were never intended to—the COX2 drugs were only developed to be safer alternatives to NSAIDs. So as far as public health was concerned, the core issue—progressive joint damage—was not being addressed. The pharmaceutical industry was merely fine tuning—albeit in an expensive way—symptom management without considering why joints were being eroded and dysfunctional.

LESSON 3. **If COX2 is regulated via gene expression and is normally dormant, why not use techniques to keep the gene dormant, rather than block the enzyme with a drug if and when it is produced?**

In other words, find out what causes the gene to be expressed (activated, copied) and then block that activity. This is the science of gene expression; what we now refer to as 'epigenetics', a name derived from the Greek for 'on top of genes'. At this point, the role of oxidants and free radicals, and the concept of oxidative stress—a concern commonly discussed in the context of ageing—becomes relevant. At the time of the rich fiscal success of COX2 inhibitors, the inflammation research community knew exactly which 'switches' regulated COX2 gene expression, their nature, number, and positioning of the docking sites on DNA of the regulatory proteins (transcription factors) that constituted these switches. It was well known these switches regulate thousands of genes involved in inflammation. Further, it was well appreciated that oxidative stress was the key trigger in activating these inflammation switches, and the impact of oxidative stress on releasing these switches from their dormant state anchored in cell cytoplasm could be traced to the nucleus and their DNA docking sites.

LESSON 4. An epigenetic approach to managing inflammation will be broader and more encompassing as it will modify and adjust a complex web of events involving thousands of genes and their connected actions.

Therapeutically, we were closing in on this core problem after extensive research in the 90s. Then, suddenly, both the nutraceutical and pharmaceutical industries diverged to contrasting approaches. The conversation shifted, we became distracted and the opportunity was shelved by the mainstream.

Divergent approaches: The era of biologics & matrix elements

For a while in the 90s, both the pharmaceutical and nutraceutical industries were coming together around the science of oxidant-driven regulation of gene expression as a fundamental driver for joint health. Then a disrupting change hit the pharmaceutical industry: the 'biologics' emerged. These are antibodies—chimeras of mouse and human—to a critical mediator of inflammation and immune activation. That mediator was TNFα (Tumor Necrosis Factor α) and the benefits were the result of soaking up all of TNFα in plasma with these antibodies, like a very efficient mop cleaning a toxic spill. These new 'biologics' brought profound success in providing relief for patients with intractable chronic inflammation, which was initially surprising as TNFα had been dominating discussions on cancer management and not chronic inflammation—hence the name. The initial therapeutic target was inflammatory bowel disease but eventually, success extended well beyond the gut to numerous systemic targets, including joint health in rheumatoid arthritis. This trend continues today with the copycat nature of commercial enterprises in response to step-wise innovation. With the success of these biologics, companies soon dropped their existing research programs on gene expression, with a rapid diversion of research resources in an attempt to catch up. In terms of product development, we had just hit a fork in the road and a new path was forged.

The nutraceutical industry had a comparable simultaneous but mechanistically different knee jerk reaction—pun intended. Ingesting matrix elements like glucosamine and chondroitin rapidly became a multi-billion-dollar industry. The theory is cartilage is relatively simple in structure; primarily, it comprises glucosamine and collagen, yielding a glassy, smooth surface to allow for joint to joint interactions. With inflammation, the cells in cartilage—the chondrocytes—become activated, releasing a family of enzymes which degrade the matrix (cartilage) in which they are embedded. These are the matrix metalloproteinases (MMPs): enzymes containing a metal, which cut up the proteins that make up the matrix, like molecular machetes. These MMPs are dangerous to have lying around so their gene is normally dormant, and the same gene switches which control inflammation also activate MMP genes.

While researchers were focusing on botanical tools to keep MMPs dormant, the nutraceutical industry opted for a simpler tactic: if matrix elements in joints are being lost, ingesting more should replace them. This concept was boosted by some initial clinical trial support and the approach became a dominant feature on the joint health landscape. While not potent, ingestible glucosamine was inexpensive and could be generated from waste materials like shrimp and crustacean shells.

LESSON 5: The nutraceutical approach of ingesting matrix elements to replace what is lost during inflammation has limited effectiveness and significant limitations.

The problem with matrix ingestibles—which have expanded from chondroitin and glucosamine to include collagen and hyaluronic acid—is there are too many assumptions associated with their ability to work, including:

- Digestion must break them down to singular elements (amino acids, glucosamine, saccharides) before they can be absorbed by the gut.
- The liver may break them down further, e.g. for glucosamine, it breaks it down to glucose and the attached amine.
- They then must be transported to the site of loss (cartilage) and then reconstructed in the exact place where they were missing, and then inserted into the matrix.
- This insertion is an active repair process, but the problem is these repair processes are normally switched off during inflammation.

Repair is done locally, using local resources with genes playing a specific role, but sadly these are not active during inflammation. To achieve active and effective repair, inflammation must first be switched off and only then can repair mechanisms proceed. Nevertheless, despite the failure of the nutraceutical industry to ask the appropriate questions, these options remain a dominant feature of joint health management. The early lessons of gene expression were pushed aside by a less technical and easier subject to communicate to the consumers. A challenge for successful marketing is one must be knowledgeable with the subject manner that one is communicating. Altered gene expression and epigenetic control of chronic disease is difficult.

Summary of historical trends within the pharmaceutical & nutraceutical industries.

The pharmaceutical route first took the approach of reducing the toxicity of COX inhibitors (NSAIDs) with the COX2 approach. That ended when the COX2 inhibitors were found to be associated with enhanced cardiovascular risk and increased risk for heart attacks and strokes. However, the biologics were shown to be effective; by soaking up a specific mediator with antibodies, they were able to dampen the inflammation response and, unlike NSAIDs, biologics have an impact on tissue injury and repair. The nutraceutical industry encouraged ingesting matrix materials in hope they would replace the elements lost to inflammation but it is now time to revisit the botanical approach to inflammation management.

LESSON 6: Look to botanicals to manage joint health through gene expression regulation.

These lessons were discovered, defined and then forgotten 20 years ago, but have great potential now due to economics, marketing, and a consumer more receptive to the concepts of gene expression and epigenetics.

Economic:

Pharmaceutical biologics are very expensive. While their benefits can be impressive for some individuals, there are also risks associated with completely knocking down a critical mediator of immunity.

Marketing:

There is a lot of discussion about epigenetics—the software of our genes—and altered gene expression in the press. It is no longer a subject too complicated to communicate to consumers. Most discussions reflect the corruption of this software with environmental influences and that not all inheritable issues are genetic (hardware mutations) but a reflection of altered control of our software. Added to this, we now know our microbiome produces metabolic products which affect our epigenome and therefore our health status.

Consumer Reception:

The greater the exposure of the general consumer to the concepts above, the more likely marketing plans will stick. Added to this is an ageing demographic in the developed world where compromised mobility is commonplace—an unmet need remains. Consumers have tried alternatives, felt they are wanting, and now seek something new that will help them with an improved quality of life, with limited toxicity compared to the alternatives; something to address the core problem at hand.

The Amazon rainforest: A botanical pharmacy replete with opportunity

Cat's claw is a vine the bark of which is made into a tea (decoction) and consumed for chronic inflammation. There are two active subspecies—*Uncaria tomentosa* and *Uncaria guianensis*—with the latter being more potent as an antioxidant and inhibitor of inflammation.[1,2] They are readily differentiated by the shape of the 'claw' in the vine with U. tomentosa being sharp, like a cat's, and U. guianensis being curled up.

"Cat's claw is a vine, the bark of which is made into a tea (decoction) and consumed for chronic inflammation.

LESSON 7: Solving chronic inflammation by correcting your genetic software

Cat's claw offers great potential for chronic inflammation through suppression of the master gene switch, NF-kB. This switch controls thousands of genes which contribute to inflammation. It prevents macrophage production of TNFα (regulated by NF-kB) with an IC50 of 10 ng/ml, which is much more potent than the more popular botanical anti-inflammatories.[3]

There are several types of switches controlling the genetic software program. NF-kB is in the class of proteins called transcription factors. Other switches are small organic molecules but both forms control which genes are turned on and which are turned off. They are vital for form and function, but they can become corrupted. This is the essence of chronic inflammation—the software is corrupted. The switches need to be activated in acute inflammation, but when that role is complete they need to return to their inactive state. Herein lies the problem with inflammation: when acute transforms into chronic, the switches remain stuck in the on position. Both the switches and the genes fail to return to dormancy resulting in tissue destruction, pain, dysfunction and a failure to repair.

Cat's claw pulls the master inflammation switch off from its docking site on DNA and returns it to its dormant state. Other botanicals and antioxidants—like astaxanthin—can act similarly, by either preventing activation or restoring dormancy. Potent antioxidants work in this manner because the release of the free, active NF-kB switch from its anchored, inactive state is mediated by oxidative stress.

With the first 'biologics', the pharmaceutical industry approach to inflammation turned on its head.

Using a foundational base of cat's claw, new products were developed, supported by multiple clinical trials focused on the management of osteoarthritis[4,5] These clinical trials were game changers for the nutraceutical industry as they were the first clinical studies to support marketing claims for benefits within seven days. Until then, the onset of benefits with glucosamine or chondroitin was two to three months. This was a mini-revolution for the joint health industry—most successful products now have a similar claim even if it is a product containing glucosamine or chondroitin. The accelerated timeline for benefits is reflective of the additional components which modify the expression of inflammation genes. However, the nutraceutical industry still struggles to explain this new timeline. It is unclear if this is a reflection of consumer intolerance to these concepts or the struggles that marketers have in leveraging the gene expression concept in their marketing plans.

The 'mechanism of actions' divergence between nutraceuticals and pharmaceuticals persists to this day. Both approaches are experiencing successful outcomes with patients.

LESSON 8: By understanding mechanisms, natural products can make a massive difference in the quality of life associated with ageing.

By understanding the importance of how nature can affect our epigenome—the software controlling gene expression—we can make a huge difference in the ageing process; not only in managing diseases like arthritis but the litany of conditions where we now appreciate that inflammation is a major causal event. But this must be driven and directed by solid science and not assumptions: for example, cat's claw is often classed as an adaptogen, and not an anti-inflammatory like botanicals including curcumin or Boswellia. An incorrect classification means many will not use cat's claw appropriately and not get the benefits that they are expecting or need.

By understanding the history, we can better appreciate how our approach to healthcare resulted in the current situation. While we are examining our history, let's not forget the history associated with cultures in the Amazon rainforest, for they have magnificent resources that could have a major impact on our quality of life. ●

Dr Mark Miller has made significant contributions as researcher, entrepreneur and marketer in the fields of health and medicine.

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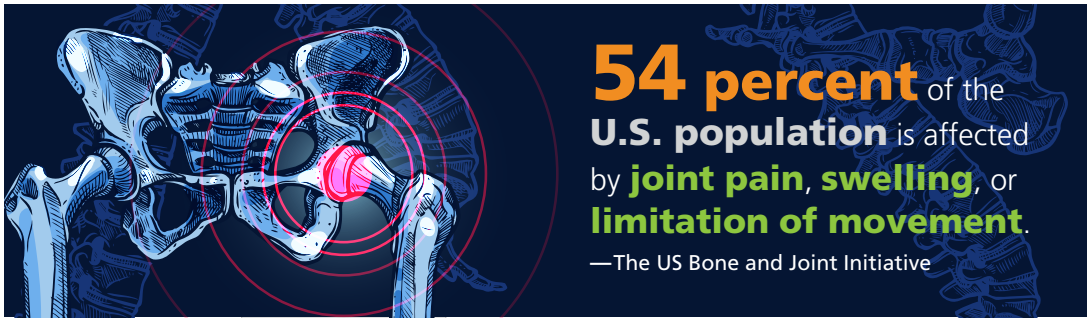
Natural Bioactives Play a Significant Role in Promoting Bone and Joint Health

by Shaheen Majeed

For baby boomers and elderly individuals, maintaining independence and quality of life continue to be top priorities. According to a 2013 report, mobility or ageing concerns ranked third and fourth among Americans aged 30 to 39 and 18 to 29, respectively.[1] Musculoskeletal conditions are the leading cause of severe long-term pain and physical disability, which affect millions of people globally. This includes conditions like lower back pain, osteoporosis, rheumatoid arthritis, osteoarthritis, and bodily injuries. Though these conditions are considered a diverse group, they share a common link anatomically as well as their association with pain and impaired physical function being largely similar.[2]

Despite being highly prevalent and having persistent impact on quality of life, until the last decade musculoskeletal conditions were nearly eclipsed in the public eye by other health conditions. As well as compromising quality of life, these conditions significantly influence the psychosocial status of affected individuals, as well as their families and caretakers. In addition, they create a major burden for health systems, and social care systems, with the indirect costs being predominant. The United Nations and World Health Organization (WHO) acknowledged the social burden and impact by endorsing the Bone and Joint Decade (2000–2010), in which a network of patients, professionals, and scientific organisations from over 60 countries aimed to improve the health-related quality of life for people with musculoskeletal disorders throughout the world.[2]

The prevalence of many of these conditions increases exponentially with age. Lifestyle factors—including obesity and lack of physical activity—also influence the quality of life for affected individuals. According to the US Bone and Joint Initiative—part of the Global Alliance for Musculoskeletal Health (previously known as the Bone and Joint Decade)—54 percent of the U.S. population is affected by joint pain, swelling, or limitation of movement.[3] In the light of increasing life expectancy and changes in risk factors, the global prevalence of musculoskeletal conditions is expected to increase significantly, requiring new treatments and the development of preventive measures.



Inflammation and bone and joint health

Inflammation is an innate defence mechanism against injury, infection, and foreign substances such as bacteria and viruses. If it starts overreacting, the same defence mechanism may begin to do harm to the body. This condition, generally termed as 'chronic inflammation,' may have harmful effects on the body, causing arthritis, for example. If the body's immune system triggers an inflammatory response without any trigger to fight-off, it may lead to autoimmune diseases (e.g., rheumatoid arthritis), wherein the body's normally protective immune system causes damage to healthy tissues.

Nuclear factor-kappa B (NF-κB) is considered the master regulator of inflammation implicated in a variety of health conditions, including musculoskeletal degeneration. NF-κB is activated whenever there is an injury or inflammatory stimuli—such as free radicals—which further leads to the activation of genes responsible for expression of cyclooxygenase-2 (COX2) enzymes—resulting in inflammation.

While it is essential to fight infections and heal injuries, the body's defence mechanism may not be able to tackle chronic inflammation and pain arising from overproduction of COX2 or any other pro-inflammatory mediators. This condition needs intervention with anti-inflammatory agents to prevent further tissue damage that could lead to severe health issues (e.g. osteoarthritic conditions).[4]

Conventional treatment limitations

Though the underlying cause cannot usually be cured in conditions like osteoarthritis and other joint problems, lifestyle changes along with therapeutic intervention may help reduce pain, improve function, and prevent further damage. Non-steroidal anti-inflammatory drugs (NSAIDs) are the conventional treatment for joint problems; however, there is evidence of side effects associated with them, and many people prefer to avoid NSAIDs. According to a survey, more than 100,000 people are hospitalized annually and 7,000 to 10,000 deaths are reported in the United States due to NSAID-related gastrointestinal complications.[5]

Natural supplements to support bone and joint health

On the other hand, well-researched natural products may be safe and effective in addressing bone and joint-related issues. Complementary and alternative therapies are one of the many treatments recommended by the US National Institutes of Health (NIH) for bone and joint-related problems such as osteoarthritis.[6] In addition, research in Ayurveda-based medicines has demonstrated that certain herbs, such as turmeric (curcumin) and *Boswellia serrata* can potentially aid in relieving the symptoms related to bone and joint problems.

Curcuma longa (Turmeric)

Turmeric is one of the most revered herbs in India's traditional system of medicine—Ayurveda—which has been increasingly validated by modern research. Other than turmeric's culinary use as a spice, it also has received much interest from the scientific and medical communities owing to its plethora of medicinal properties. However, the mechanism of action and chemical components responsible for the therapeutic activity of turmeric have only recently been investigated. Studies have demonstrated multiple health benefits of turmeric are due to the three major phenolic compounds present—namely curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC)—collectively known as 'curcuminoids.'[7]

Owing to their proven anti-inflammatory and antioxidant properties (targeting multiple inflammatory signalling molecules while also demonstrating activity at the cellular level), curcuminoids are known to regulate inflammation, cell growth, and apoptosis, thus being effective in managing conditions like arthritis.[8,9]

Clinical Study 1

Objective: To evaluate the efficacy of curcuminoids supplementation in reducing oxidative stress by measuring the levels of serum concentration of important biomarkers in patients with knee osteoarthritis (OA).

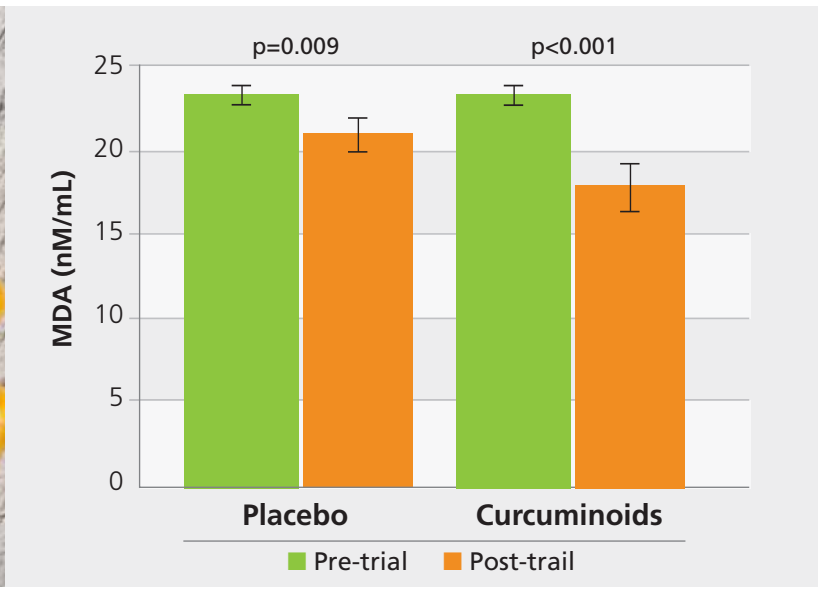
In this randomised, double-blind, placebo-controlled, parallel-group, six-week trial, 53 subjects diagnosed with knee OA were included in the trial and were divided in two groups. Subjects were supplemented with either 1,500 mg of curcuminoids (as Curcumin C3 Complex® from Sabinsa) and 15 mg of the bioavailability enhancer piperine (as BioPerine® from Sabinsa) daily or matching placebo.

In this sub-study, changes in serum levels of oxidative stress biomarkers as a secondary efficacy measure of supplementations with curcuminoids were evaluated in both the groups.

Serum samples evaluation demonstrated in the curcuminoids group, oxidative stress was significantly reduced with increase in serum levels of superoxide dismutase (SOD) and glutathione s-transferase (GSH), and concurrently there was a decrease in the malondialdehyde (MDA) concentration (Fig. 1).

Conclusion: Supplementation with curcuminoids attenuated systemic oxidative stress in osteoarthritic patients, thus being helpful in relieving OA symptoms.[10]

Effect of Curcuminoids on MDA Levels



Clinical Study 2

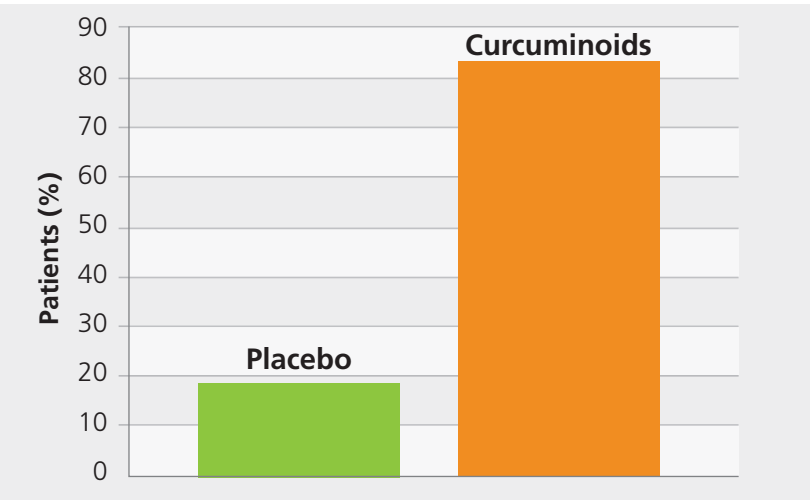
Objective: To investigate whether clinical benefits with curcuminoids are associated with a significant alteration in circulating biomarkers of systemic inflammation including pro-inflammatory cytokines.

This was a sub-study of the previous randomised, double-blind, placebo-controlled, parallel-group clinical trial. Forty subjects with mild-to-moderate degree knee OA were randomly allocated to receive either curcuminoids (1,500 mg/d in three divided doses; Curcumin C3 Complex®) or matched placebo for six weeks. A natural bioavailability enhancer piperine (15 mg/d in 3 divided doses; BioPerine®) was added to the treatment regimen. Naproxen was allowed during the study for managing intolerable pain. Efficacy measures determined in this sub-study were: changes in serum levels of interleukin (IL)-4, IL-6, tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), high-sensitivity C-reactive protein (hs-CRP), and erythrocyte sedimentation rate (ESR).

A significant decline in serum concentration of IL-4 (P=0.001), IL-6 (P=0.006), and hs-CRP (P=0.004) was seen in the curcuminoids group at the end of the study. However, serum levels of TNF-α and TGF-β and mean ESR remained unaltered. According to patient reports, 84% of subjects reduced the use of naproxen in the curcuminoids group, whereas only 19% subjects in the placebo group reduced the use of the analgesic. This difference was significant between the study groups (P=0.001)(Fig. 2)

Conclusion: This study showed the beneficial effects of curcuminoids are due to a local anti-inflammatory effect in the osteo-cartilagenous tissue.[11]

Reduced Use of Pain Killer Drug



Boswellia serrata

Boswellia serrata—commonly known as Salai or Salai guggul—is a moderate-to-large sized branching tree belonging to the family Burseraceae. This tree is native to the Arabian Peninsula and India, and is known for a gum resin called olibanum, or frankincense. This resin is traditionally known to possess anti-inflammatory, anti-arthritic, antirheumatic, and analgesic properties.[12]

The anti-inflammatory properties of this gum resin are attributed to the presence of four major boswellic acids, of which acetyl-11-keto-β-boswellic acid (AKBBA) is the most potent. Though boswellia shows anti-inflammatory action much

like conventional NSAIDs it has the unique property to block two pro-inflammatory enzymes: 5-lipoxygenase (5-LOX) and human leukocyte elastase (HLE), and thus help in managing various inflammatory conditions that are perpetuated by leukotrienes. Additionally, unlike NSAIDs, long-term usage of boswellia does not lead to irritation or ulceration of the stomach. It is clinically proven to be safe and effective in the management of arthritic conditions and knee pain.

Zingiber officinale (Ginger)

Ginger is a rhizome belonging to the family *Zingiberaceae*, originating in South East Asia. Traditionally, it is used as herbal medicine for the management of several inflammatory conditions and degenerative disorders, like arthritis and rheumatism.[13] Several clinical studies have demonstrated effectiveness of ginger in alleviating symptoms of arthritis and joint pain.

Bone and joint health has become a growing concern around the world, especially due to the growing ageing population coupled with widespread prevalence of inflammatory joint conditions like arthritis. Natural alternatives are preferred by many consumers due to their safety and efficacy profile in comparison to conventional NSAIDs. Hence, a range of natural supplements, which are clinically well-established, are available in the market that may be useful to soothe inflamed joints and providing symptomatic relief in arthritis and joint pain. ●

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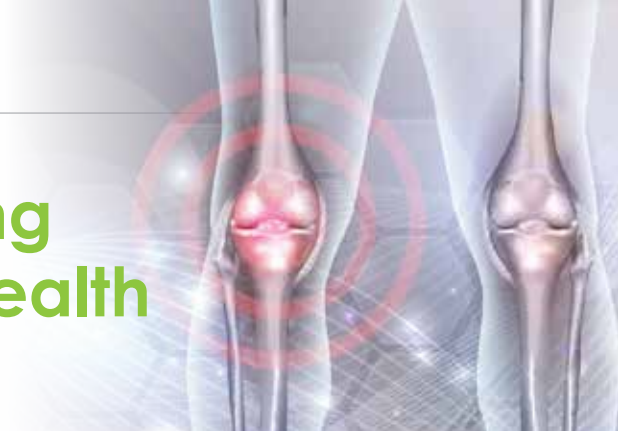

Vitamin K2: The Missing Ingredient for Bone Health

by Jim Beakey

Good bone health, starting early in life, creates a path to life-long longevity and well-being. Childhood and adolescence mark an intensive period of bone-building until 'peak bone mass' is reached around age 20. Bone mass and strength then begin a natural and expected decline. This decline is typically steeper for women than for men as menopause triggers hormonal changes that affect bone health. The skeleton is also in a continual state of change, fully replacing itself about every seven years. Bone health—and nutrients to support bone health—are vital and often overlooked components of general health and wellness.

Calcium is widely understood to be the building-block of strong bones. The importance of vitamin D3 is also gaining awareness. D3 facilitates the absorption of calcium through the intestine and into the bloodstream where it can then be put to work for bone-building. The 'missing ingredient' for bone health—at least until recently—was vitamin K2. Though discovered over a half century ago, K2 was largely overlooked until clinical investigation began in earnest in the early 2000s. K2 was only first synthesized in 2011—decades behind its peers in the fat-soluble vitamins group (A, D, E and K1). Absent comprehensive clinical study and a synthesis method (an important milestone in the commercial development of a vitamin), K2's critical role in bone health was late to be understood.

Vitamin K2 regulates the transport of calcium in the body and activates osteocalcin proteins which incorporate calcium into the bone matrix. Without K2, calcium and D3 are unable to optimally support bone health. This vitamin has been the least-appreciated ingredient in this 'bone health triangle', but this is beginning to change as K2 takes centre stage.

Bone metabolism – invest early, live long and healthy

Bones are organs—they are comprised of living tissue. Within the hard, rigid outer shell, bones have a lightweight inner matrix that consists of a network of collagen fibers. Minerals such as calcium phosphate provide structural integrity and rigidity in the outer layer and the fiber matrix provides flexibility. Bone also contains nerves and blood vessels within the voids of the matrix. Finally, the bone matrix contains specialised cells that build-up new bone and remove old bone—the mechanisms of resorption and regeneration for this organ. About every seven years, bone remodeling leads to a complete replacement of the skeleton. These dynamic, constantly changing organs require specific minerals and nutrients to maintain their healthy form.

Early in life, new bone is created faster than old bone is broken down. Peak bone mass is reached sometime after the age of 20 when it levels off, and then ultimately begins a natural age-related decline. After that, the balance tips towards in favour of the cells that break down bone, and old bone is broken down at a rate faster than it is replaced. Bone density and strength then start to decline. Bones become more porous, lighter and less dense. The risk for

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fractures increases and the body's ability to mend broken bones decreases. The highest risk for fractures comes from bone-weakening conditions such as osteopenia and osteoporosis, most commonly associated with women or certain medical conditions.

The good news is that studies demonstrate that even a 10 percent increase in peak bone mass by the end of adolescence can lead to a 50 percent decrease in the risk of osteoporotic fracture in later years.[1] Strong, healthy bones formed in early life set a higher baseline for when the natural decline in bone mass begins. This highlights the importance of sufficient dietary intake of calcium, vitamin D3 and vitamin K2 during both early and late stages of life.

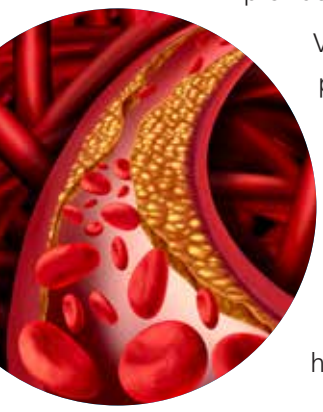
Strong, healthy bones

formed in early life set a higher baseline for when the natural decline in bone mass begins.

K2: Putting calcium in balance

Vitamin K2 is an essential fat-soluble vitamin, just like vitamins A, D and E. The members of the vitamin K family can be defined as phylloquinone (vitamin K1) and menaquinone (vitamin K2). There are 13 members of the K2 family, each defined by the length of their molecular side chain. Menaquinone-7 (MK-7) is the most relevant for bone health as it is best absorbed and is most bioactive. MK-7 is essential for the activation of osteocalcin. Activated osteocalcin binds with calcium in the blood and transports the calcium to the osteoblasts—cells that use calcium to build bones.[2] Vitamin K2 is a necessary co-factor in the carboxylation reaction that activates osteocalcin. The long half-life of MK-7 compared to other MK forms (about 72 hours vs. 1.5) and superior absorption ensures optimal osteocalcin activation.

After calcium is delivered to the bone matrix, some osteocalcin enzymes are free to return to the blood. The ratio between active (carboxylated) and inactive (uncarboxylated) osteocalcin is used as a marker for vitamin K status.[3] Low blood measures of carboxylated osteocalcin indicate an increased need for vitamin K2. As most western diets are likely K2-deficient, supplementation provides a means to improve calcium utilisation for bone building.



Vitamin K2 also activates another important calcium-regulating protein called matrix Gla protein (MGP). While calcium is vital for bone health, too much can be a problem as excess calcium can be deposited in the cardiovascular system. This causes a hardening of vessels and arteries and a loss of flexibility as calcium plaques build. The heart must then work harder to push blood through stiffened, reduced diameter vessels, increasing cardiovascular risk factors. Activated MGP binds excess calcium in blood to prevent deposition in the circulatory system. Vitamin K2 has even been shown to reverse existing levels of calcification and restore flexibility to vessels and arteries. K2 helps transport calcium to where is it needed, and away from where it can be harmful.

K2: Diet or supplementation?

Most people are likely to be K2 deficient. Certain fermented foods, such as some cheeses and soybean dishes (Japanese natto), are naturally high sources of K2. Since most western diets are low in these foods, dietary K2 requirements are primarily met by less efficient MKs (MK-4, MK-8, MK-9). Some MK-7 is also created in the body by a bacterial process in the gut, but not enough. Speculation as to how this deficiency developed centres on changes in food production and storage brought about in the past 100 years by industrialisation. Widespread refrigeration and the use of preservatives likely reduce natural fermentation in food, and grain-fed livestock do not benefit from natural fermentations of grasses in the stomach which produce MKs. While MK-7 intake levels across countries has yet to be explored, studies of western populations show that only half of K2-dependent proteins are typically activated, suggesting low vitamin K2 status.[4-9]

The good news is that K2 deficiency can be overcome by supplementation. K2 supplementation increases the amount of activated osteocalcin and MGP proteins in the body.[10] For example, a study with healthy volunteers demonstrated that, prior to supplementation with vitamin K2, levels of inactive osteocalcin were high; afterwards, they were low and most of the osteocalcin was activated.[11] To achieve adequate osteocalcin activation, research indicates a daily dosage of 90 to 120µg of vitamin K2 is required.[7,9] Studies have shown populations reaching the recommended daily dose—such as Japanese people who consume natto dishes—were shown to have lower rates of bone and heart diseases.[12] Further epidemiological studies in Japan also support the notion that MK-7 promotes bone health.

Clinical support for k2 bone health

The bone health benefits of MK-7 derived from diet have been demonstrated in several epidemiological studies. In northern regions of Japan, the fermented soybean dish natto (rich in MK-7) has been consumed for hundreds of years. Studies have attributed good bone health and fracture risk reduction to a diet high in vitamin K2. Natto is even approved as a health food in Japan.

In northern regions of Japan, the **fermented soybean dish natto (rich in MK-7)** has been consumed for hundreds of years.

Clinical studies demonstrate that vitamin K2 supports bone growth[13], reduces bone fracture risk[12, 14] and increases bone mineral density (BMD) compared to a control group.[15] Vitamin K2 has been shown in clinical studies to improve BMD in healthy postmenopausal women and protect postmenopausal women against bone loss.[8, 15] In an important three-year clinical trial, bone strength was investigated in 244 healthy postmenopausal women. Test and control groups were supplemented with 180µg of MK-7 or placebo. The study demonstrated that MK-7 supplementation significantly reduced levels of inactive osteocalcin (ucOC) and increased

the level of activated osteocalcin (cOC). In addition, the intake of MK-7 significantly decreased the age-related decline in bone mineral content (BMC) and density (BMD) measured at the thighbone and lumbar spine. MK-7 also significantly reduced the loss in vertebral height.

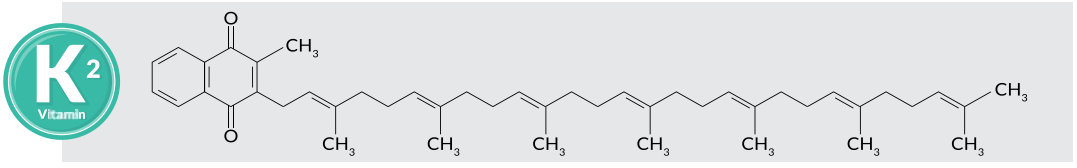
In another placebo-controlled clinical trial, bone microarchitecture was investigated in 148 postmenopausal women with osteopenia, a condition characterized by low bone mineral density.[16] After one year of MK-7 intervention, Rønn and colleagues showed that MK-7 preserves the bone microstructure compared to the placebo group.

Finally, high levels of uncarboxylated osteocalcin are linked to lower BMD and an increased risk of hip fractures.[17-19] In sum, these studies demonstrate a solid evidence base for the beneficial bone health effects of vitamin K2 MK-7.

Commercialisation of K2 – Which K2 is best for supplementation?

About 30 percent of K2 ingredient manufacturing is produced by synthesis and the remainder by a fermentation production process. Synthesis produces an extremely pure, crystalline, all-trans MK-7 molecule, with no other MK forms present. Synthesis achieves isomeric purity of 99.7 percent or higher. While this is noteworthy, the K2 market enjoys healthy competition among several manufacturers of high-purity MK-7 produced via the fermentation method. However, as many of the studies and clinical trials investigate MK-7 from diet (e.g. natto) or fermentation-derived MK-7, the question arises as to which source of K2 provides the optimal bone-health benefits?

At the molecular level the answer is simple. Both production methods produce an identical molecule, and this molecule is identical to the one found in nature. More importantly, the molecules created by the two manufacturing methods are 100 percent equal in biological activity and function. A 2016 study demonstrated that synthesis-derived MK-7 is 100 percent bioequivalent to fermentation-derived MK-7.[20]



The purity achieved by synthesis, however, does provide one commercial advantage. K2 is a fat-soluble vitamin. In 1948, the US Federal Security Agency discovered when combined with calcium, fat-soluble vitamin D can degrade 'within a month or two.' A similar problem was discovered following the launch of the first K2-plus-calcium products. Testing demonstrated that these first K2-plus-minerals products were not shelf-stable. Even the purest, highest-quality K2 MK-7 proved unstable when combined with minerals like calcium or magnesium – regardless of manufacturing method.

This unfortunate discovery posed significant problems for K2 as K2's primary function is as a mediator of calcium. Therefore, while K2-plus-calcium product formulations are tailor-made to support bone health, the K2 will begin to degrade—weakening the bone health benefits of the product over time. Protection of the MK-7 molecule via microencapsulation proved a solution to this challenge. Protection of the K2, separating it from incompatible co-ingredients, prevents degradation or oxidation and ensures shelf life. While purity itself is not a factor for K2/mineral stability, microencapsulation requires a starting point of 100 percent purity.

K2 commercial opportunities

The bone and heart health benefits of vitamin K2 MK-7 are applicable to virtually every consumer type and several top-selling market categories. Mothers and infants, children and teens, and men and women from their 20's to their 90's all require K2 for different reasons at the various stages of life. K2 offers product extension and upgrade opportunities for market categories that also leverage bone and heart health, including the multivitamin, women's health, healthy ageing and even sports nutrition. K2 is being investigated for a wide range of other indicators as well, such as effects on cancer risk reduction (prostate), male testosterone levels and cognitive protection against the effects of Alzheimer's and Parkinson's diseases. K2 even shows promise in the health and beauty category as an anti-wrinkle agent and in the prevention of varicose veins. The future of K2 looks bright as this 'missing ingredient' is re-discovered.

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Takeaways for Your Business

The osteoarticular system structurally provides the organism with balance and movement, and involves different types of elements, bones and soft tissues. Those which represent an essential part of joints—ligaments and cartilages included—are specialised tissues joining structures linked to movement, so they should have characteristics that provide resistance and elasticity—collagen and elastic fibres.

Bones, which provide the structural basis of the organism, are made of calcified tissue formed by inorganic substance, organic substance and specialised cells interdependent with each other. Collagen takes centre stage in the structure of bones, since it is present in 90 percent of the organic matrix, with glucosamine and chondroitin (the proteoglycans) comprising the remaining 10 percent.

The complexity of the osteoarticular system requires special attention—a good diet and regular exercise are vital in the prevention of osteoarticular conditions including osteoarthritis and osteoporosis. Many joint conditions are caused by chronic inflammation. Cat's claw is a vine—the bark of which is made into a tea (decoction) and consumed for chronic inflammation—offering great potential through the suppression of the master gene switch, NF-kB. This switch controls thousands of genes which contribute to inflammation. Other botanicals and antioxidants—like astaxanthin—can act similarly, by either preventing activation or restoring dormancy. Potent antioxidants work in this manner because the release of the free, active NF-kB switch from its anchored, inactive state is mediated by oxidative stress.

Other well-researched natural ingredients for bone and joint health include curcumin and ginger. Turmeric (*Curcuma longa*) is one of the most revered herbs in India's system of medicine—Ayurveda—due to the three major phenolic compounds present: the curcuminoids. By targeting multiple inflammatory signalling molecules while also demonstrating activity at the cellular level, curcuminoids are known to regulate inflammation, cell growth and apoptosis, making it effective in managing conditions like arthritis. Ginger is a rhizome used as a traditional herbal medicine for the management of several inflammatory conditions and degenerative disorders, including rheumatism. Several clinical studies have demonstrated ginger's effectiveness in alleviating symptoms of joint pain. Natural ingredients are preferred by many consumers due to their safety and efficacy profile in comparison to NSAIDs.

Vitamin K2 is another ingredient with great market potential. While calcium is widely understood to be the building block of strong bones, and vitamin D is known to facilitate the absorption of calcium into the bloodstream, vitamin K2 is only now being clinically investigated for its role in bone health. Vitamin K2 regulates the transport of calcium in the body and activates osteocalcin proteins which incorporate calcium into the bone matrix—without K2, calcium and vitamin D are unable to optimally support bone health. As most people are likely to be K2 deficient, there is market opportunity in most categories and age groups as K2 deficiency can be overcome by supplementation.

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