

Musculoskeletal Support Formula



IV
VERSION

Joint Support

A True Innovation in Joint Care

Joint Support has been the leader in joint support nutritional supplements since it first came out in 1999. Version IV represents the fourth evolution of this supplement. Multiple ingredients in Joint Support work along synergistic pathways to decrease inflammation and promote the body's natural synthesis and maintenance joints, ligaments, muscles and tendons, it protects, prevents and helps in the repair of musculoskeletal injuries and inflammation, regardless of the cause.

www.mdjointsupport.com

MD+ JOINT SUPPORT VERSION IV



Joint Support is formulated to support muscle, cartilage and joint function in many ways.

1. By maintaining tissue integrity it helps prevent musculoskeletal problems.
2. By providing the mechanisms and stimulus for repair of injured or damaged musculoskeletal tissue, whatever the cause.
3. By offering relief for aches and pains.

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<http://www.mdJointSupport.com>



The previous version of Joint Support was already the leader in joint support products. The new Joint Support version IV dramatically improves the protective, supportive and tissue building effects and creates a new paradigm in musculoskeletal support formulas.

What's Changed in Joint Support version IV?



Joint Support has been the leader in joint support nutritional supplements since it first came out in 1999. Version IV represents the fourth evolution of this supplement. Each formulation is an improvement over the previous one, taking into consideration my experience with the previous version and the most recent research and findings, and applying these to make Joint Support even more effective.

I added a number of ingredients as well as fine tuning some of the ingredients already in Joint Support version III. I tried several dozen variations of ingredients and dosages to determine the optimum number and dosages of ingredients necessary to dramatically improve on the already spectacular effects of Joint Support on musculoskeletal tissue.

I added

1. Pyridoxal-5-phosphate
2. Alpha Lipoic Acid
3. Carnosine
4. Coenzyme Q10
5. Pau D'Arco
6. Proline

I increased the amounts of

1. Vitamin D
2. BioCell Collagen II
3. MSM
4. Stinging Nettle Extract
5. Quercetin
6. Rutin
7. Turmeric Extract

All were increased significantly, some more than four fold over the previous formula.

The result of the additions and fine tuning is a much more effective product. The five tablets per dose has gone up to six tablets per dose and a bottle of Joint Support now contains 180 tablets instead of 150.

Although much more expensive to manufacture I've kept the retail price the same as an incentive to the serious supplement user to use the very best Joint Support formula on the market at a bargain basement price. Just compare the number and dosages of the

ingredients in Joint Support with any other joint support formula on the market and you'll be convinced on just how much of a bargain Joint Support really is.

History of Joint Support

As a medical doctor involved in dealing with degenerative diseases and in sports injuries for four decades I've tried all kinds of ways to both prevent and treat musculoskeletal problems, dealing with both acute and chronic inflammation, pain and repair that are part and parcel of musculoskeletal problems and diseases.

The underlying common factor in all of these conditions, whether acute or chronic, is inflammation. Inflammation, although a normal and necessary response to injury, is responsible for a range of acute and chronic diseases. That's because if it's excessive or inappropriate it gives rise to a number of inflammatory compounds that in turn cause excessive damage to tissues.

For example, inflammatory compounds such as the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF- α), the interleukins IL-1, IL-6 and IL-8, and pro-inflammatory eicosanoids such as PGE2, cause a catabolic response in tissues, promote degeneration and hinder healing. Using compounds that mitigate or block the effects of these pro-inflammatory compounds, several of which are included in Joint Support, can both prevent the progression and help heal even the damage seen in degenerative joint disease.¹

Another aspect of maintaining healthy joints has to do with anabolic influences such as locally controlled growth factors. For example several studies have shown the importance of insulin-like growth factor as a promoter of growth and extracellular matrix (ECM) synthesis by chondrocytes in healthy articular cells.^{2,3}

Over the years I searched for natural ways to deal with musculoskeletal problems, ways that replaced or at least complimented traditional ways of dealing with these problems, including drugs and surgery.

I was also looking for something natural that had minimal side effects, was convenient to use and that worked.

All of my knowledge and research has finally come to fruition in Joint Support, a supplement that really works and is safe. In fact, not only safe but a supplement that naturally increased musculoskeletal health and helped deal with injuries and degenerative conditions such as arthritis.

This amazing, patent-pending formula produces an entirely new level of effectiveness when compared to all of the other Joint Support products on the market. In fact, it is the first product ever to look at all aspects of preventing and healing musculoskeletal problems and contains dozens of ingredients that work synergistically to produce

The ingredients in this evidence-based, research-driven formula have been proven to decrease inflammation, increase healing, and maintain without causing any negative health effects.

Joint Support is a product of my four decades of research and involvement in the medical and sports fields. It is a true Joint Support breakthrough that is unequalled in its ability to provide significant recuperative and regenerative effects.

It's so good that Joint Support is **used by hundreds of elite Olympic athletes and top bodybuilders** to optimize musculoskeletal health, prevent overtraining effects, and heal injuries, thus increasing health and performance.

With Joint Support they're able to maximize performance by decreasing the adverse effects of training to the max without overtraining and both preventing and healing injuries and muscle aches and pains.

Joint Support offers the advantages of some of the more potent anti-inflammatory, pain reducing, healing, and tissue anabolic drugs, without any of the side effects.

What can I expect from the use of Joint Support?

Joint Support is not just another one dimensional joint support product. It's a nutritional breakthrough designed to attack and decrease inflammatory and catabolic processes, while at the same time increasing anabolic processes. By influencing multiple pathways it helps support, maintain and rebuild the whole musculoskeletal system.



Joint Support:

1. **Supports and maintains musculoskeletal health**
2. **Supports cartilage regeneration**
3. **Reduces injuries and joint degeneration**
4. **Accelerates healing and decreases down time**
5. **Reduces inflammation**
6. **Eases musculoskeletal aches and pains due to acute and chronic injury and degeneration such as arthritis**
7. **Reduces joint and muscle stiffness**
8. **Helps heal injuries by reducing catabolic influences and promote tissue rebuilding**
9. **Enhances mobility and flexibility**
10. **Offers a safer alternative to prescription drugs**

Joint Support supplies nutritional support to the various joint and muscle structures by supplying nutrients known to be involved in the maintenance, repair, and reformation of these structures.

As such, it's an excellent supplement for supporting the musculoskeletal system as both a preventative supplement to help you prevent joint injury in the first place, and as a supplement to help to decrease pain and heal injuries and other musculoskeletal problems including the rebuilding of joint cartilage.

In regards to arthritis Joint Support is designed to decrease inflammation and thus aid in the relief of pain and slow the onset of the degenerative effects of osteoarthritis. In the case of injuries adding Joint Support to your supplement regimen can increase healing and speed recover, thereby reducing downtime after an injury.

The bottom line is that Joint Support will help you to maintain the health of your joints and muscles, and deal with a variety of musculoskeletal problems due to injury, aging and disease.

Athletes and Joint Support



The human body is a magnificent piece of machinery with pulleys, rubber bands, hinges and joints throughout. And while most of the time it functions magnificently, it can be stressed and even broken in places. In fact, muscle and connective tissues are major sources of physical discomfort and disability, especially in athletes.

This is not surprising, considering the stress that training imposes on muscle and connective tissues, the most abundant and widely distributed tissues in the body.

We can all understand the importance of muscle tissue in athletes; however the role of connective tissue is often under appreciated. It shouldn't be since it forms our bones, surrounds our organs, holds our teeth in place, forms cushions and lubricates our joints, and connects the muscles to our skeleton. In fact, collagen is the most abundant protein, comprising of ~30% of total protein in the body.

Soreness from exercising is a familiar experience, often an accepted incidental result of training. Most soreness results from muscle tissue trauma, but stress is also induced upon the tissues connected to the muscles: bones, tendons and ligaments. These tissues are also subject to aging.

Most connective tissue injuries involve damage to the structural components of the tissue. In sports activities, injuries are classified into two types: acute and overuse injuries. Acute trauma occurs from lacerations and partial or complete rupture of the tissue. Overuse injuries, the most common category, result from chronic overloading or repetitive motion. The capacity of the tissue for repair greatly exceeds degradation and cellular metabolism is altered such that damage occurs at the cellular and structural levels.

Inflammation is the most prominent symptom of both types of injuries. While inflammation is a natural part of the healing process in any injury, chronic inflammation may lead to increased tissue degradation and impair the repair process. Indeed, chronic inflammation is a major factor in several connective tissue diseases, especially within articular joints.

Pharmaceuticals are often used to manage or alleviate symptoms occurring with connective tissue inflammation. However, many of these substances may alter the healing and repair process, and offer only temporary relief. In fact, many of the medications used cause side effects, such as gastrointestinal upset and may even accelerate joint degradation in the long run.⁴

Many natural ingredients and remedies have been used over the centuries that have not only alleviated symptoms of tissue stress, but also shown to help rebuild tissue and restore function in joints. Many of these natural substances aid in recuperation, help heal sore muscles and joints, increase recovery from injuries such as strains and sprains, and help strengthen musculoskeletal support tissues.

The use of these substances, as well as various vitamins, minerals, antioxidants, amino acids, and others, if used in a proper and timely fashion, have a positive effect on the immune system, overtraining and both preventing and treating injuries. They can also be useful in treating musculoskeletal pain, inflammation and degenerative/arthritis conditions.

Joint Support is the best example of a comprehensive, multifaceted, synergistic supplement that can be useful for all of these conditions.

Joint Support is formulated to support muscle, cartilage and joint function. It helps maintain healthy joints and relief for aches and pains after exercise. By providing ingredients that are essential for the body's natural synthesis and maintenance of joints, ligaments, muscles and tendons, it aids in protection against the effects of excessive exercise, and aids in the healing of musculoskeletal injuries and degeneration.

Ingredients in Joint Support.

BioCell Collagen II™



Water and large molecules fill the spaces in-between the cells and collagen fibers. Its viscosity acts as a lubricant due to the high water content. One of the major components of the ground substance are the proteoglycans and structural glycoproteins, which trap water molecules and lend strength, rigidity and resiliency to the extracellular matrix.

Proteoglycans are large molecules formed by many linear chains of polysaccharide units called glycosaminoglycans (GAGs). GAG chains radiate out from a protein core like bristles of a bottlebrush. Sulfation and the complexes of the GAGs determine their biological activity. These complexes, which may contain hundreds of attached proteoglycan aggregates, constitute a significant role in cartilage tissue.

Proteoglycans act as a molecular sieve moderating the movement of cells, and nutritive and inflammatory substances. They are also responsible for attracting and maintaining water balance within the tissue. The high density of negative charges of these molecules attracts and binds water molecules. Because they attract and hold water, they form a 'sponge' that, when compressed, absorbs force and distributes it equally. This is how cartilage protects structures in the joint from mechanical (stress and weight) damage.

BioCell Collagen II™ provides low molecular weight compounds, which are readily and easily absorbed into the bloodstream. The components of BC II including **chondroitin sulfate**, **hyaluronic acid (HA)**, and **glucosamine sulfate** can support proteoglycans and glycosaminoglycans (GAG's) in the joint matrix thereby increasing synovial (joint) fluid and supporting cartilage synthesis in the joints.

The low molecular weight compounds present in Biocell Collagen II™ are more biologically available and more effective than the higher weight compounds present in many other preparations. For example a recent study found that low molecular weight preparations of chondroitin sulfate had preventive effects on arthritis in a murine model.⁵

The amino acid profile of BioCell Collagen II™ is rich in the primary amino acids, such as **arginine**, **proline** and **glycine** that make up the type II collagen molecule and as such is conducive to collagen formation and repair.

BioCell Collagen II™ has been clinically shown to significantly reduce pain syndromes in subjects with various forms of arthritis, spinal pain and other joint pain.

For more information on BioCell Collagen II™ see http://www.metabolicdiet.com/pdfs/biocell_collagenII.pdf.

Glucosamine Sulfate

Glucosamine sulfate is one of the basic substrates for synthesis of these important macromolecules in connective tissue. The synthesis of glucosamine from glucose and glutamine is the rate-limiting step in GAG production, and hence in repairing cartilage.

Following cartilage trauma or tearing, the body may not be able to make enough glucosamine for optimal healing. In addition, the ability to convert glucose to glucosamine declines with age because of a reduction in the amount of the enzyme glucosamine synthetase.

Taking glucosamine supplements can increase GAG levels significantly.⁶ Clinical trials have shown that glucosamine sulfate attenuates arthritic changes and relieves the pain and inflammation of osteoarthritis.^{7,8,9} It also represents a safe alternative to nonsteroidal anti-inflammatory medications (e.g., ibuprofen), which have been shown to inhibit repair and accelerate destruction of cartilage.¹⁰

A recent review concluded that glucosamine is better tolerated than most other NSAIDs such as ibuprofen or piroxicam, and in short-term clinical trials, glucosamine provided effective symptomatic relief for patients with osteoarthritis of the knee. In addition, glucosamine has shown promising results in modifying the progression of arthritis over a 3-year period.¹¹

Several studies have shown the beneficial effects of glucosamine on articular cartilage.

A study published in 2002 done on athletic horses found that glucosamine inhibited cartilage catabolic responses and also prevented IL-1beta-induced increases in nitric oxide production, prostaglandin E2 and proteoglycan release.¹²

A recent study showed that glucosamine was effective in improving function and decreasing pain in people who experienced knee pain likely as a result of prior cartilage injury and/or arthritis.¹³

In an earlier study, 68 athletes with cartilage damage in their knees were given 1500 mg of glucosamine sulfate daily for 40 days, then 750 mg for 90 to 100 days.¹⁴ Of the 68 athletes, 52 had a complete resolution of symptoms and resumed full athletic training. After four to five months, athletes were able to train at pre-injury rates. Follow-up exams 12 months later showed no signs of cartilage damage in any of the athletes.

It's been shown that glucosamine sulfate provides pain relief and improved function in knee osteoarthritis (OA).¹⁵ In a recent 3-year study on 212 patients with knee OA glucosamine was associated with a significant reduction in joint space narrowing.¹⁶

At present glucosamine is one of the recommendations now made by physicians for athletes and non-athletes alike in the management of injuries and arthritis. For example, in a recent article physicians included the use of glucosamine in the medical management of early osteoarthritis of the knee in athletes.¹⁷

Chondroitin Sulfate

Chondroitin sulfate is a major component of cartilage. It is a very large molecule, composed of repeated units of glucosamine sulfate. Like glucosamine, chondroitin sulfate attracts water into the cartilage matrix and stimulates the production of cartilage. Likewise it has the ability to prevent enzymes from dissolving cartilage.

Although the absorption of chondroitin sulfate is lower than that of glucosamine (lower molecular units are better absorbed), a few recent studies have shown very good results from long-term treatment with chondroitin sulfate, reducing pain and increasing range of motion.

For example, a one-year long, double-blind clinical study gave 800 mg of chondroitin sulfate to 42 patients of both sexes, aged 35-78 years with symptomatic knee osteoarthritis. The chondroitin sulfate was well tolerated and significantly reduced pain and increased joint mobility.

A recent review looked at the published reports with a view of determining the usefulness of chondroitin sulfate.¹⁸ The authors concluded that chondroitin sulfate plays a role in articular and bone metabolism by controlling cartilaginous matrix integrity and bone mineralization.

There is some controversy about the absorption of chondroitin sulfate and thus its usefulness. Recent studies, however, have confirmed its absorption and oral bioavailability.^{19,20}

Combined Use of Glucosamine and Chondroitin Sulfate

Several studies have shown the beneficial effects of glucosamine and chondroitin sulfate on the musculoskeletal system.

They have been used as drugs to treat osteoarthritis in Europe and are now gaining popularity in the US. Clinical trials both in the US and abroad, on both humans and animals have confirmed their benefits and safety.

The GAGs have been shown to repair and improve joint function as well as providing pain relief in chronic sufferers. A recent study found that the combination of chondroitin and glucosamine was more effective than chondroitin alone.²¹

A study published in the New England Journal of Medicine in 2006 found that **the combination of glucosamine and chondroitin sulfate** was more effective for patients with moderate to severe pain secondary to osteoarthritis of the knee than the popular prescription drug celecoxib (recently implicated in an increased incidence in cardiac problems including congestive heart failure), one of the new cyclooxygenase (COX)-2 inhibitors that are widely used for treating arthritis.²²

Other recent studies have found effects of both glucosamine and chondroitin sulfate on gene expression.²³ For example one study found that glucosamine had effects on pretranslational mediators of osteoarthritis, an effect that may contribute to its cartilage-sparing properties. Other studies have found that both glucosamine and chondroitin sulfate when used orally may regulate expression of matrix degrading enzymes and their inhibitors at the transcriptional level,

A recent study looking at the effects of both glucosamine and chondroitin on cartilage cells concluded that “by enhancing the "protective" metabolic response of chondrocytes to stress, glucosamine and chondroitin sulfate may improve its ability for repair and regeneration.”²⁴ In a later study the authors found that glucosamine had preventative effects on arthritis in rats.²⁵

A meta-analysis looking at all the available studies on glucosamine and chondroitin studies found that both, and especially glucosamine, were effective for the alleviation of pain, inflammation and in maintaining and improving the structural integrity of joints.²⁶

Thus, glucosamine alone or in conjunction with chondroitin sulfate, because of the safety profile and effectiveness, along with other supportive substances are fast becoming the first treatment of choice for many joint and connective tissue pain and inflammation sufferers.

Joint Support because of it's large number of proven ingredients working both additively and synergistically

Hyaluronic Acid

BioCell Collagen II™ naturally contains ultra high concentrations (min. 10%) of low molecular weight hyaluronic acid, which is vital for the health of soft connective tissue where it is a major component of the extracellular matrix (ECM), and is present in synovial joint fluid, cartilage, the eye, and in skin tissue both dermis and epidermis.

Hyaluronic acid is unique among the GAGs in that it does not contain any sulfate and is not found covalently attached to proteins as a proteoglycan. It is, however, a component of non-covalently formed complexes with proteoglycans in the ECM. Hyaluronic acid polymers are very large (with molecular weights of 100,000 - 10,000,000) and can displace a large volume of water. This property makes them excellent lubricators and shock absorbers. Hyaluronic acid may be able to slow down chondrocyte apoptosis (cartilage cell death) in OA by regulating the processes of cartilage matrix degradation.

Interestingly enough, BioCell Collagen II, besides providing HA directly, also actively inhibits hyaluronidase (as does **echinacea**), an enzyme that breaks down hyaluronic acid. This inhibition further increases HA levels in tissues.

Methylsulfonylmethane (MSM)

MSM stands for methylsulfonylmethane, a stable odorless metabolite of DMSO. MSM, a natural form of organic sulfur found in low concentrations in our bodies. Along with glucosamine sulfate, it is a basic substrate for the synthesis of connective tissue. Many claims have been made for MSM, including relief from arthritis, muscle pain, joint pain and inflammation, beneficial effects on the immune system, and scar tissue reduction, and there are a few studies that support these claims.^{27, 28}

A recent paper looked at the possibility that MSM may exert some effect on inflammation and arthritis secondary to increases in serum sulfate.²⁹

Alpha Lipoic Acid

Alpha lipoic acid (ALA) has potent antioxidant properties intrinsically and secondary to its ability to increase levels of intra-cellular glutathione, and its ability to recycle other antioxidants such as vitamin C, vitamin E and glutathione.^{30,31,32,33,34}

ALA was also added to Joint Support because of its actions on decreasing both the pro-inflammatory cytokines^{35,36} and because of its effects on decreasing secondary cortisol elevations.

It has been shown to inhibit cross-linking among proteins, a process that contributes to the aging process in the body and especially in collagen-heavy tissues such as skin. Alpha-lipoic acid activates a collagen-regulating factor known as AP-1 that turns on enzymes that digest glycation-damaged collagen and thus make the skin more supple and youthful looking.

Besides having potent antioxidant and anti-inflammatory effects, ALA also has significant anabolic effects secondary to its beneficial effects on insulin sensitivity and growth hormone and IGF-I secretion, all factors involved in maintaining, repairing and regenerating musculoskeletal tissues.^{37,38,39,40}

As well, it helps neutralize and remove various toxic metals, including mercury, from the body.

Amino Acids

Amino acids contribute to musculoskeletal health and repair in many ways. For example, **proline** and **glycine** are essential for collagen production. Both are in the BioCell Collagen II™, and extra glycine is also added to the Joint Support formula. Proline is the precursor to hydroxyproline, an essential ingredient in collagen production and thus in joint and tendon health and repair.

Methionine is a sulfur bearing amino acid and is necessary for cartilage formation. It has been shown to stabilize joint cartilage and protect joint tissue from damage, and also has shown to be useful in the treatment of rheumatoid arthritis.

Arginine aids in the release of growth hormone, a powerful hormone that aids in collagen tissue repair. As well, arginine increases nitric oxide formation, which causes vasodilatation and improves circulation promoting the healing of damaged tissues and wounds. It has also been shown to act as a mild analgesic and relieve pain. A recent report in *The Lancet* (Vol. 352, July 25, 1998) suggests that it may help promote healthy tendons and help promote soft tissue repair.

Taurine, a sulfur-containing amino acid and the second most abundant amino acid, and the most abundant free amino acid, found in skeletal muscle tissue.

A recent study on rats has shown that oral taurine supplementation may increase muscle performance and reduce muscle injury caused by exercise.⁴¹ The aim of the study was to determine if increasing muscle levels of taurine would decrease free radical damage after exercise-induced injury. The authors found that first of all taurine levels rose in muscle after supplementation, and secondly that running performance was improved by the taurine supplementation. Thus it appears taurine supplementation may facilitate exercise performance and reduce some of the counterproductive muscle injury caused by exercise.

Taurine has been shown to increase GH in animals.⁴² As well it is a potent antioxidant, increases insulin sensitivity, increases cell volume and therefore protein synthesis, and acts as a cytoprotective agent in the central nervous system and muscle.^{43,44,45,46,47} Overall, while it isn't used to make up musculoskeletal tissue, it has significant anabolic effects.

Histidine may also play a role in joint health by decreasing inflammation and perhaps in other ways. It's thought that people suffering from arthritis benefit from supplemental histidine because of the effects it may have in reducing inflammation associated with joint disease and other musculoskeletal disorders.

Antioxidants

Antioxidants form a front line defense against cell damage caused by free radicals, which are involved in muscle, joint and tendon damage and inflammation, degenerative arthritis and even in the aging process. The use of antioxidants can reduce free radical damage that occurs when we exercise and can also attenuate the ongoing damage to injured tissues caused by free radicals, thus accelerating the healing process.

Antioxidants, such as **vitamins C and E** (see under Vitamins below), **selenium**, **green tea**, **reduced glutathione** and **N-acetyl-cysteine (NAC)**, all present in Joint Support, can play an important role in reducing inflammation and fatigue, decreasing tissue damage, and in both preventing and treating injuries.

Various antioxidants, such as vitamin E, have been found to be useful in the treatment of some forms of arthritis⁴⁸ and in dealing with the oxidative stress of exercise.⁴⁹ As well, oxidative damage has been shown to contribute to the pathogenesis of injuries and arthritis, and the use of antioxidants, such as NAC,⁵⁰ shown to have therapeutic value for reducing endothelial dysfunction, inflammation, fibrosis, invasion and cartilage erosion.

A recent study found that a combination of 2 antioxidants, **selenomethionine** and **epigallocatechin-gallate** (the main antioxidant in **green tea extract**), had beneficial effects on catabolic and anabolic gene expression of articular chondrocytes.⁵¹ The authors of the study concluded that “Our data provide insights into the mechanisms whereby ECGg and selenium modulate chondrocyte metabolism. Despite their differential mechanisms of action, the 2 compounds may exert global beneficial effects on articular cartilage.”

Boswellia Serrata Extract

The gum resin of boswellia serrata, also called salai guggal, has been used as an herbal treatment for rheumatoid arthritis and other inflammatory conditions for centuries in Ayurvedic medicine. Boswellia inhibits pro-inflammatory mediators, such as leukotrienes, and reduces degradation of glycosaminoglycans in connective tissues.

Both tissue and animal studies have demonstrated the anti-arthritic properties of Boswellia extracts.^{52, 53} The latest study found that a herbal dietary supplement consisting of a natural resin extract of Boswellia serrata was effective for the symptomatic relief of osteoarthritis in dogs⁵⁴

Clinical studies including humans with inflammatory conditions and administered Boswellia reported improvements after 7 days. The extracts also were well tolerated by patients.

Bromelain, Papain, Trypsin and Rutin

Oral agents containing various natural enzymes, including bromelain, trypsin, and papain, and rutin, have been used in Europe to treat injuries and arthritis. Such enzyme combinations may reduce inflammation and cartilage damage. Several studies in animals have shown beneficial effects from the use of these enzymes.

In Joint Support I included four proteolytic enzymes that I feel are the most useful - the endopeptidases bromelain and papain, the flavonoid rutosides (rutin) and the hydrolase L-trypsin. All four are effective proteolytic enzymes and have been used in the oral treatment of injuries and arthritis.⁵⁵

These proteolytic (protein-digesting) enzymes aid in modulating inflammation several ways. They aid increase absorption of other substances and help to degrade inflammatory debris in the body. Repair commences at a faster rate while inflammation is contained. All four have been documented as being useful for reducing inflammation, swelling and pain and increasing recovery.^{56,57,58,59,60,61,62,63,64}

Cayenne Pepper

Capsaicin, the primary active ingredient in cayenne, is involved in pain mediation and has anti-inflammatory properties. It also has a protective effect on the lining of the stomach. As well, it has beneficial effects on circulation and protective effect on the lining of the stomach.

Carnosine

Carnosine, a dipeptide made up of the amino acids alanine and histidine (histidyl-alanine) was added to InsideOut because of its many beneficial effects. It has been shown to have significant antioxidant and anti-inflammatory properties, increase healing, enhance the immune system, and provide anti-aging effects.^{65,66,67,68,69,70}

It also inhibits glycation, a destructive protein/sugar reaction that occurs in the body and which contributes to aging through a number of mechanisms including the breakdown of connective tissue, a loss of elasticity, and a decrease in cellular hydration. Carnosine, along with alpha lipoic acid, provides protection against glycation and premature aging.

Coenzyme Q10

Coenzyme Q10 is one of the key antioxidant nutrients that protect mitochondrial membrane lipids and proteins and mitochondrial DNA from free radical-induced oxidative damage. It also regenerates and extends the action of vitamin E thus further protecting against membrane lipid peroxidation. Under the various forms of stress and inflammation, demand for coenzyme Q10 increases which must be met by dietary intake in order to optimize mitochondrial function.

Devil's Claw Root (Uncaria Tomentosa)

Africa is home for this traditional herbal medicine. Growing wild in desert soils, its large, sharp, claw-like fruit is a nuisance and danger to grazing cattle, hence its name. The root of the Devil's Claw plant is harvested at the end of the rainy season. Today it is widely used alone or in combination with other herbs to treat arthritis, rheumatism, gout and other inflammatory diseases.

Devil's Claw possesses anti-inflammatory properties that are derived from its active ingredients of harpogoside and beta-sitosterol. In its traditional uses, patients report relief of pain, swelling and joint discomfort.

The modern research on Devil's Claw is less than complete, however it is well recognized and prescribed in many European medical clinics. Some lab studies have reported that it

possessed anti-inflammatory and analgesic properties similar to the drug phenylbutazone, but some other studies failed to observe this action. This inconsistency may stem from a lack of understanding on the exact mechanism of its medicinal actions.

Side effects are rare, but it is not recommended for pregnant women or those suffering from ulcers. A standardized extract is 5% harpogosides and 100 mg daily is a typical dosage.

Ginger

Ginger (*zingiber officinale*) is described in Ayurvedic medicine to be useful in inflammation and rheumatism. Sources suggest that one of the mechanisms by which ginger shows its therapeutic effects could be related to inhibition of prostaglandin and leukotriene biosynthesis, thereby working as a dual inhibitor of eicosanoid biosynthesis.⁷¹ The bioactive constituents (the main one being [6]-gingerol) have been shown to inhibit the enzymes that facilitate production of several pro-inflammatory factors. A recent study has shown a favorable comparison between ginger and ibuprofen (a popular arthritis medication).⁷² Besides its anti-inflammatory effects, ginger has been shown to be a powerful antioxidant.⁷³

Ginger has also been shown in a small clinical study to decrease pain, increase mobility and reduce swelling and stiffness.

Ginkgo Biloba

Ginkgo biloba herb is extracted from the Ginkgo biloba tree and has many useful effects including increasing blood flow to various tissues, and works against free radicals. It has been shown to improve blood circulation to the skin, brain, hands, feet and legs.⁷⁴ It's also a potent antioxidant and has significant anti-inflammatory effects.⁷⁵

Terpenes in ginkgo biloba appear to block Platelet Activating Factor. PAF is a chemical messenger that causes inflammation and problems with blood vessels. It's also a potent antioxidant and as such helps protect tissues from oxidative damage.

Green Tea Extract

The constituents of green tea are polyphenolic compounds termed catechins. The most abundant catechin in green tea is (–)-epigallocatechin 3-gallate (EGCG) although others are also present in lesser quantities.

Green tea extract, besides being rich in antioxidants, also has significant effects on inflammation and the musculoskeletal system.^{76, 77, 78} For example green tea catechins have been shown to inhibit inflammation and cartilage degradation, and have therapeutic effects on a variety of musculoskeletal problems including arthritis.^{79, 80, 81, 82, 83}

Green tea extract may well prove to be more useful than green tea itself. A recent study found that green tea extract supplements retain the beneficial effects of green and black tea and allow larger doses of tea polyphenols to be used without the side effects of caffeine associated with green and black tea beverages.⁸⁴

Melatonin

Melatonin, a hormone produced by the pineal gland located at the base of the brain, has many important properties and effects. It is a potent antioxidant (in one study it was found to have greater antioxidant effects than vitamins E and C, and reduced glutathione⁸⁵), regulates the sleep/wake cycles, and increases growth hormone secretion. All of these effects can result in significant effects on injury prevention and healing.

It has also been shown to be useful in treating insomnia and sleep disturbances related to conditions like fibromyalgia and depression. As such it is useful for decreasing the stress that often accompanies musculoskeletal injuries and other problems. As well, aspirin and other NSAIDs can decrease melatonin levels and thus increases the need for some supplementation.

Omega-3 and Omega 6 Oils – GLA, DHA and EPA -

Synthesis of collagen involves a cascade of biochemical modifications of the original building blocks. Many enzymes, cofactors and growth promoters influence these modifications, which are crucial to the structure and function of mature collagen and other tissues so important to integrity of joints and other connective tissue.

Dietary fatty acids are precursors for hormones and determine the composition of our cell membranes, influencing the production of pro- and anti-inflammatory substances. Omega-3 fatty acids, found in fish oils (mainly **EPA** and **DHA**) and flaxseed oil, have been shown to reduce oxidant stress⁸⁶ (oxidative stress or free radical damage is a factor of importance in the development of musculoskeletal inflammatory events) and suppress the production of pro-inflammatory compounds in the body⁸⁷ and therefore influence inflammatory conditions such as arthritis.⁸⁸

The literature documents relief of tender joints and morning stiffness associated with arthritis, thus reducing the need for non-steroidal anti-inflammatory drugs (NSAID).^{89,90} Also, there was no gastrointestinal upset that is typically associated with chronic NSAID use.

A recent review concluded that the available data show consistent and reproducible beneficial effects of omega-3 (n-3) fatty acids on bone metabolism and bone/joint diseases.⁹¹ European clinical trials have shown a synergistic effect of fish oil and vitamin E in reducing pain in patients with rheumatoid arthritis.⁹²

Gamma linolenic acid (GLA) has shown anti-inflammatory properties and decreases some of the pro-inflammatory cytokines such as TNF-alpha and IL-1 beta.⁹³ In one study arthritic patients using GLA had reduced joint pain and stiffness and improved grip strength.

Pau D'Arco

Pau d'arco, or the inner bark of the tabebuia avellaneda tree, is native to Brazil, where it is used traditionally to treat a wide range of conditions including pain, inflammation and arthritis.

Preliminary laboratory research examining the properties of pau d'arco is beginning to suggest that the traditional uses may have scientific merit. Such laboratory studies have shown that pau d'arco has pain killing, diuretic, anti-inflammatory, anti-infectious, anti-psoriatic, and anti-cancer abilities. Taking this early data, combined with information collected about traditional uses Pau d'arco may reduce inflammation of the musculoskeletal system associated with injury and arthritis.

Rutin and Quercetin

These two flavonoids have been shown in recent studies to have significant anti-inflammatory activity in cases of both acute and chronic inflammation.⁹⁴ A recent review article concluded that there is evidence to suggest that flavonoids may be beneficial to connective tissue for several reasons, which include the limiting of inflammation and associated tissue degradation, the improvement of local circulation, as well as the promoting of a strong collagen matrix.⁹⁵ These compounds also have significant antioxidant properties.

Quercetin may have properties that downregulate or inhibit cyclooxygenase-2 safely.⁹⁶

S-Adenosyl-L-methionine (SAME) – Increasing Endogenous Production

Methyl donors are important for the methylation reaction, which adds a methyl group (one carbon atom and three hydrogen atoms), on proteins, enzymes, chemicals, DNA, and amino acids like homocysteine. Methylation is important for maintaining many functions in the body including genetic expression, and neurological and musculoskeletal function.

Usually, this methylation process occurs through a compound called S-adenosyl-L-methionine (SAME). However, SAME, because of its volatility and incompatibility, can't be incorporated into a multi-ingredient formula such as Joint Support so the alternative is to include ingredients that have been shown to increase endogenous production and at the same time reduce the increased levels of homocysteine that can follow.

SAMe, is synthesized from the amino acid methionine and its level in the body is increased by dietary methyl donors such as **follic acid, B12** (especially the **methylcobalamin** that is used as the preferred form of B12 in Joint Support rather than the synthetic cyanacobalamin, the usual form of B12 found in most other supplements), **B6** and **betaine** (trimethyl glycine). These nutrients are also needed to reduce homocysteine levels and decrease cardiovascular disease.

Various clinical trials and animal studies suggest that SAMe may be effective, among other things, in reducing pain and inflammation in the joints, in promoting cartilage repair, and helping with arthritic symptoms.^{97,98} It's also felt to have significant direct and indirect (by increasing glutathione synthesis) antioxidant effects.⁹⁹

Some of these studies have shown that SAMe supplements were as effective as NSAIDs in people with arthritis in diminishing morning stiffness, decreasing pain, reducing swelling, improving range of motion, and increasing walking pace. Several of the studies also suggest that SAMe, while as effective as NSAIDs, has fewer side effects.¹⁰⁰

Shark Cartilage

Shark cartilage may have benefits in accelerating the healing of cartilage. Studies have shown that shark cartilage can play a scavenger role for reactive oxygen species and protect against DNA lesions and as such degenerative joint diseases.^{101,102} Also shark cartilage has been shown to have some analgesic and anti-inflammatory effects.^{103,104} As well, shark Cartilage has been shown to inhibit angiogenesis and stimulating immune function.

Silicon

Silicon is considered an essential trace element and is required for the formation of skin, ligaments, tendons, cartilage and bone.¹⁰⁵ This is thought to be due to its role in the enzyme polyhydroxylase, which is responsible for the formation of collagen in bone and elastin, cartilage and other connective tissues. Silicon may also be important in bone calcification.

Stinging Nettle Extract

Nettle extracts have long been used as an adjunct treatment for arthritis in Europe and is not beginning to gain popularity in the United States. Cell studies using extracts of nettle leaf have demonstrated a variety of active substances that inhibit prostaglandin production and cytokine secretion.

Tumor necrosis factor-alpha (TNF- α) and nuclear factor are factors associated with chronic inflammatory conditions. These factors as well as another cytokines such as interleukin-1B (IL-1B) have been identified as factors that aid the destruction of cartilage in

osteoarthritis and rheumatoid arthritis. Nettle leaf significantly reduces the concentration of these factors, thus improving arthritic conditions as seen evidenced in human clinical trials.¹⁰⁶

Turmeric

Curcumin, the active component of turmeric, is documented to have anti-inflammatory and antioxidative benefits.¹⁰⁷ As an antioxidant, curcumin reduces the activity of certain enzymes, inhibiting all branches of the arachidonic acid cascade. Thereby, these plant extracts reduce inflammation.

Turmeric exhibits marked anti-inflammatory action and has been shown to be as effective as some anti-inflammatory drugs. For example in a double-blinded trial, post surgical patients receiving curcumin experienced reductions in stiffness and joint swelling comparable to the effects of phenylbutazone, a potent anti-inflammatory drug.¹⁰⁸

Of all the spices and herbal preparations it seems that only the spice turmeric has any anti-inflammatory effects. This was the conclusion of a study of a variety of Ayurvedic and herbal preparations, which was presented recently at the 9th Asia Pacific League of Associations for Rheumatology Congress.

In this study, a variety of herbal and Ayurvedic preparations were tested in rats. The rats were fed oral doses of the varied herbal and Ayurvedic recipes. Only turmeric showed anti-inflammatory effects when tested on irritated paws of the rats.

As well, turmeric has also been shown to have protective effects against chemical damage to connective tissue.¹⁰⁹

Vitamins and Minerals

Recovery and repair of tissues require a host of vitamins and minerals that participate in synthesis of new cells and tissue. For example, certain vitamins and minerals are required to facilitate the formation of endogenous anti-inflammatory compounds, including **Vitamin B6, Vitamin E, Vitamin C, niacin, zinc, selenium** and **magnesium**. Many vitamins and minerals also serve as antioxidants and help protect cells against the oxidative damage produced by inflammation.

Vitamin C is necessary for collagen synthesis and is a strong antioxidant with beneficial effects on pro-inflammatory cytokines.¹¹⁰ Research on vitamin C shows that it may have important effects in reducing pain and inflammation secondary to exercise. In one study 400 mg daily of vitamin C reduced post exercise pain and inflammation.¹¹¹ Vitamin C is involved in the enzymatic hydroxylation of proline to form 4-hydroxyproline, an amino acid that is an integral part of collagen and elastin.

As well as being an antioxidant, **vitamin E**, has been demonstrated to reduce pain in arthritic patients. Both of these vitamins are important in treatment of arthritic conditions, as shown in studies, possibly by reducing oxidative stress induced by TNF- α . And both of these vitamins are also helpful in reducing muscle soreness secondary to exercise. Clinical studies report that supplementing with vitamin E and C reduce post-exercise inflammation and pain in muscles and joints.

Several clinical studies have shown the anti-inflammatory effects of **vitamin B3** (as **niacinamide**) and its benefits of in both rheumatoid and osteoarthritis. **Pantothenate** or vitamin B5 has been shown in several studies to influence wound healing and collagen synthesis. Some studies have also shown that low levels of pantothenic acid (vitamin B5) are inversely related to increased joint pain and stiffness.

Niacinamide also directly increases GH secretion. Niacinamide, along with the amino acid **glycine** (which also has an effect on GH secretion), also have some relaxing effects and thus are useful before bed to help sleep.

Vitamin B6 involved in macronutrient metabolism, GH and IGF-I secretion, tissue anabolism, and the production of neurotransmitters including dopamine, noradrenaline and serotonin.

Joint Support has both **pyridoxine** (in the form of HCL) and **pyridoxal-5-phosphate** (P5P) in it. P5P is the metabolically active form of vitamin B6. Pyridoxine HCL, while as easily absorbed as P5P has to be converted to P5P in the body in order to be used by the enzymes involved in protein metabolism and various hormonal processes. P5P is the preferred form of vitamin B6 as it can be used directly in the body without relying on the livers conversion of other forms of vitamin B6 into P5P. As well, less is needed to achieve the same cofactor effects.

Ample amounts of **vitamin B12** are also included in Joint Support, at levels 10 times the amount found in most other products. As well, the B12 is in the form of **methylcobalamin**, the metabolically active form of B12, which is better absorbed and used by the body compared with the synthetic cyanocobalamin,, the less expensive form of B12 usually used in nutritional supplements.

Methylcobalamin, as well as other methyl group donors such as **folic acid**, **betaine**, **methionine**, with the aid of **vitamin B6** (all in Joint Support), have multiple functions in the body including increasing the formation of SAME (see above) and the conversion of homocysteine (high levels are a risk factor for cardiovascular disease) to the essential amino acid methionine.

Minerals are required for normal cell function and several serve as cofactors in the many enzymatic processes involved in synthesis of connective tissue macromolecules. **Calcium** and **phosphorus** (in the form of phosphates), and **vitamin D** to regulate both, are important for joint and bone health. Vitamin D In addition to its effects on calcium metabolism, also plays a role in the normal turnover of articular cartilage.

Boron and **manganese** are critical cofactors for collagen and GAG synthesis and metabolism. Some pharmaceuticals are known to negatively interact with some minerals. Supplementation of these minerals should ensure adequate supply in the body.

Clinical evidence suggests that **zinc** deficiencies have a high impact on connective tissue synthesis. **Zinc** primarily acts as cofactor in many enzyme systems that regulate cell proliferation and growth and in immune integrity. Diminution of collagen synthesis and strength as well as impaired healing is seen in animal tissues with zinc deficiencies.

Copper is a co-enzyme for lysyl-oxidase, which is essential for the conversion of collagen and elastin, and subsequently for joint function. It also has anti-inflammatory properties and may ease pain in arthritic and damaged joints.

White Willow Bark

Salicin, a glycoside present in most willow tree bark, has been a known source of pain relief since Hippocrates. Derivatives of salicylates are widely used for their analgesic and anti-inflammatory properties. Aspirin is the best known of these compounds, and salicin is its precursor. The most accepted mechanism of action proposed for the salicylates is inhibition of prostaglandin biosynthesis. Aspirin and other salicylates inhibit cyclooxygenase enzymes, which are responsible for conversion of arachidonic acid to prostaglandins, mediators of inflammation.

A recent study showed that aspirin and fish oil together had a more favorable effect on the pro-and anti-inflammatory factors than aspirin alone.¹¹² Also, the natural sources of salicin have fewer side effects than aspirin.

Yucca Leaf Extract

Yucca contains natural steroid like compounds that have anti-inflammatory, analgesic and antioxidant properties. These saponins also block the release of toxins from the intestines that inhibit normal formation of cartilage. Yucca has also been shown to have some anti-tumor effects.

Other Ingredients

Lemon Myrtle Leaf is used by the Aborigines of Australia for arthritis because of its anti-inflammatory properties.

Thyme-Leaved Gratiola is an herb is traditionally used in inflammation and rheumatism.

Withania Somnifera (ashwagandha) also known as Indian Ginseng, is often used to reduce arthritic pain and inflammation. It has been shown to have beneficial effects on the immune system and decrease levels of pro-inflammatory cytokines.^{113,114}

Summary

MD+ Joint Support will safely reduce stress on musculoskeletal tissues and speed up recovery without the side effects associated with many of the drugs used in modern medicine. The many natural ingredients in Joint Support may also reduce many such side effects when used along with NSAIDs as well as act in concert with other treatments to prevent acute musculoskeletal damage and potentially reverse chronic injuries and inflammation. As such, **Joint Support** not only gives symptomatic relief, but also intervenes at the origin of the problem and helps rebuild tissue.

For recreational and competitive athletes where injuries and sore muscles reduce and may even interrupt training time and participation in sports events, Joint Support will reduce healing time and increase recovery and performance. As well, the use of Joint Support when training hard helps prevent injuries and decrease the chances of overreaching turning into overtraining.

Joint Support IV Nutritional Panel

Supplement Facts:		Serving Size: 6 Tablets		Servings Per Container: 30	
	Amount Per Serving	% Daily Value		Amount Per Serving	% Daily Value
Vitamin C (as Ascorbic Acid)	200 mg	333%	Lignisul MSM (Methyl-Sulfonyl-Methane)	1000 mg	*
Vitamin D (as Cholecalciferol)	200 IU	50%	Shark Cartilage	500 mg	*
Vitamin E (as d-Alpha Tocopheryl Acetate)	150 IU	500%	Stinging Nettle Extract (<i>Urtica dioica</i>) (leaf)	300 mg	*
Vitamin B3 (as Niacinamide)	50 mg	250%	Quercetin Dihydrate	200 mg	*
Vitamin B6 (as Pyridoxine HCL and Pyridoxal-5 Phosphate)	10 mg	500%	Turmeric Extract (<i>Curcuma Longa</i>) (root)	150 mg	*
Vitamin B12 (Methylcobalamin)	500 mcg	8,333%	Rutin	100 mg	*
Folate	500 mcg	125 %	Joint Support™ Proprietary Complex 3000 mg		
Vitamin B5 (as D-Calcium Pantothenate)	10 mg	100%	Alpha Lipoic Acid, Ashwagandha Extract (<i>Withania somnifera</i>) (root),		
Calcium (as Calcium Phosphate)	200 mg	20%	Betaine HCL, Boswellia Serrata Extract (<i>Boswellia serrata</i>) (resin),		
Magnesium (as Magnesium Phosphate)	100 mg	25%	Bromelain, Carnosine, Cayenne (<i>Capiscum annuum</i>) (fruit), Cellulose,		
Zinc (as Monomethionine) (OptoZinc®)	10 mg	67%	Co-enzyme Q10, Devil's Claw Extract (<i>Harpagophytum procumbens</i>) (root),		
Copper (as Copper Gluconate)	100 mcg	5%	Ginger Extract (<i>Zingiber officinale</i>) (root),		
Selenium (as Selenomethionine)	25 mcg	35%	Gingko Biloba Extract (<i>Gingko biloba</i>) (leaf),		
Manganese (as Manganese Sulfate)	5 mg	250%	GLA, Glutathione (Reduced), Glycine, Green Tea Extract (<i>Camellia sinensis</i>) (leaf),		
BioCell Collagen II®	1200 mg	*	Jujube Extract (<i>Ziziphus jujube</i>) (fruit), L-Histidine, L-Arginine, L-Methionine,		
Hydrolyzed Collagen Type II	720 mg*		L-Trypsin, Lemon Myrtle (<i>Backhousia citriodora</i>) (leaf), Melatonin,		
Chondroitin Sulphate	240 mg*		N-Acetyl-Cysteine, Omega-3 Fish Oil Powder (EPA, DHA), Papain USP,		
Hyaluronic Acid	120 mg*		Pau D'Arco (<i>Tabebuia avellanedae</i>) (inner bark), Proline, Silicon dioxide,		
Boron (Amino Acid Chelate)	2 mg	*	Taurine, Thyme-Leaved Gratiola (<i>Bacopa monnieri</i>) (whole plant),		
Glucosamine Sulfate	500 mg	*	White Willow (<i>Salix alba</i>) (bark), Yucca Extract (<i>Yucca filamentosa</i>) (whole plant),		
Other Ingredients: Stearic Acid, Modified Cellulose Gum, Hypromellose, Magnesium Stearate.					
*Daily Value not established					

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