# Introduction to Nutrition and Supplements for Plantar Fasciitis and Chronic Foot Pain Disorders

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Introduction

According to a 2014 study by the American Podiatric Medical Association, more than 83% of 1,000 Americans surveyed said that they experience chronic foot pain.¹ Chronic pain in your feet is not only agonizing, but it also impedes your daily routine. Those who suffer from chronic foot pain are all too familiar with the stabbing-like sensation that occurs in their heels, toes, arches, and even ankles. There are many factors that lead to chronic foot pain including lack of proper footwear, injury, and even degenerative disorders. While common pain-relieving medications like aspirin or ibuprofen might offer temporary relief, it doesn't fix the root of the problem. Treating your chronic foot pain can have multiple approaches. One of the most overlooked is nutrition and how it plays a role in easing and treating the root cause of many types of foot pain.

There is extensive research and evidence to suggest that nutritional supplements may be an effective way to cure not only chronic foot pain, but other ailments as well. While the evidence is there, nutritional supplements are still not widely used in a clinical setting. Costly, and sometimes unsafe or ineffective prescription drugs and therapies are still the method of choice for treating chronic foot pain. This White Paper aims to look at alternative treatment methods by focusing on a nutrition-based approach to curing chronic foot pain.

#### What Causes Chronic Foot Pain?

Foot pain can be caused by a variety of reasons and can occur at any age. Depending on its severity, chronic foot pain can affect other parts of your body, like your hips and back. Chronic foot pain can manifest in different ways, but the link between most foot pain disorders is inflammation. Inflammation is an immune response to injury or foreign agents in the body (like viruses or toxic chemicals). When your body suspects harm, your immune system sends out inflammatory cells and cytokines (proteins in the body that stimulate more inflammatory cells). These cells then work to trap bacteria and other foreign agents or begin to rebuild injured tissue.

Visible symptoms of inflammation can include pain, swelling, bruising, or redness. However, inflammation can also affect your body internally in ways that aren't visible. Inflammation is a natural bodily response to pathogens or injury and is in most cases good for us. Acute inflammation may last a couple of weeks until the body has healed itself before symptoms disappear. Chronic inflammation is when symptoms do not disappear, even after the injury or illness has healed. In some people, inflammation may be present when there is an absence of injury or illness.

Chronic inflammation can cause numerous adverse bodily reactions. It's been linked to many different health conditions, including autoimmune diseases. Autoimmune diseases cause your body to attack healthy cells, mistaking them for foreign agents. 4 This leads to a continuous inflammatory response that wreaks havoc on your physical and sometimes mental health. Symptoms of chronic inflammation can include:

Constant fatigue

- Body pain
- Joint stiffness
- Swelling
- Frequent infections
- Mood disorders, like depression and anxiety
- Weight gain
- Gastrointestinal issues
- Numbness and tingling of certain body parts
- Skin problems like rashes

Overtime, chronic inflammation can start damaging your body's healthy cells, tissues, and organs. This can lead to tissue death, internal scarring, and DNA damage. Serious diseases can result from chronic inflammation, including cancer, rheumatoid arthritis, type 2 diabetes, heart disease, obesity, asthma, and dementia (in older adults).

#### What Causes Chronic Inflammation?

The most common cause of chronic inflammation is autoimmune disorders, but chronic inflammation may also be caused by exposure to toxins or result from an untreated infection or injury. Lifestyle factors can also contribute to inflammation. Drinking too much alcohol, obesity, infrequent or too frequent exercising, chronic stress, and smoking are all contributing factors that can lead to inflammation in the body. Additionally, eating certain foods or allergens can also lead to an inflammatory response.

### **Inflammation and Foot Pain**

Foot pain disorders are often linked to inflammation, thus solving inflammation may help to solve most foot pain disorders. Some of the most common foot pain disorders include plantar fasciitis, peripheral neuropathy, gout, rheumatoid arthritis, and tendonitis.

#### **Plantar Fasciitis**

The plantar fascia is a thick band of tissue that connects your heel to your toes. When this band of connective tissue becomes inflamed, it results in a condition known as plantar fasciitis.

Plantar fasciitis causes sharp, stabbing pain in the bottom of your foot closer to your heel. The pain is most apparent in the morning or when you take your first steps, however it can be triggered by long periods of standing or when you stand after sitting for a while. It can also be painful during exercise. This pain is due to small tears in the fascia that can occur when too much stress or tension is placed upon it. Your plantar fascia is shaped like a bowstring and supports the arch of your foot by absorbing shock when you walk. Repetitive actions that cause stretching or tearing in the fascia results in the development of plantar fasciitis.

Risk factors for Plantar Fasciitis include:

- **Age** is a common contributor in developing plantar fasciitis. The elderly have had many more years to put wear and tear on their fascia, especially if they spent a lot of time on their feet. They are also more at risk for cardiovascular diseases and diabetes (both of which can reduce circulation to the feet), as well as degenerative disorders.<sup>7</sup>
- Certain physical activities or exercises that put a lot of stress on your heels can lead to the development of plantar fasciitis. Ballet, long-distance running, or working long hours where you're required to stand (such as retail employees, factory workers, and teachers) are examples of activities that could be risk factors for chronic heel pain.
- **Natural foot shape**, like a high arch or flat feet can affect the way weight is distributed when walking, which can put added stress on your plantar fascia.
- **Obesity** forces your feet to carry excess weight which can put too much pressure on your plantar fascia, leading to chronic inflammation and pain.

# **Peripheral Neuropathy**

Peripheral neuropathy is a condition that results when there is damage to the peripheral nerves located outside the brain and spinal cord. Symptoms of peripheral nerve damage most often include painful, tingling sensations in the hands and feet. This sensation can be accompanied by numbness, muscle weakness, circulatory problems, and sometimes paralysis. In some cases, symptoms of neuropathy can improve or disappear. This is most likely in cases of peripheral neuropathy that are caused by treatable conditions. In cases where neuropathy can't be cured, treatment is aimed at reducing symptoms through a combination of medicines and therapy.

Common causes of peripheral neuropathy include:

● **Autoimmune disorders** like Guillain-Barre syndrome, lupus, and rheumatoid arthritis.

- **Diabetes** is the most common cause of peripheral neuropathy. It's estimated that at least half of those diagnosed with diabetes will experience some form of neuropathy in their lifetime.
- **Vitamin deficiencies** can sometimes lead to nerve damage. Your body needs adequate nutrients in order to function properly. People who are malnourished or suffer from conditions that make them unable to absorb nutrients properly are more at risk for developing neuropathy.
- **Alcoholism** can lead to vitamin deficiencies, thus increasing the risk of developing neuropathy symptoms.
- **Viral or bacterial infections** such as Lyme disease, shingles, and HIV can cause neuropathy.

#### Gout

Gout is the name for a form of arthritis that causes severe, sudden attacks of pain in one or more joints, typically in the big toe. It's characterized by redness, swelling, and tenderness so extreme that even the slightest touch can cause intense pain. Gout attacks can occur at any time and happen to anyone. The best way to treat gout is to manage symptoms and prevent flare-ups. The cause of gout attacks is due to a build-up of urate crystals in your joint that trigger inflammation. Urate crystals are formed when you have high levels of uric acid in your blood, which is created from the breakdown of purines. Purines are natural chemical compounds found in foods such as red meat, anchovies, mussels, alcoholic beverages, and fruit juices. When your body produces too much uric acid or is unable to excrete enough through your kidneys, sharp, needle-like urate crystals are formed in your joints that cause the pain and tenderness associated with gout attacks.

# Risk factors for gout include:

- **Diets rich in red meat**, shellfish, fructose (sugar from fruit) and alcoholic beverages (especially beer) can increase levels of uric acid in your blood, therefore increase your risk of gout.
- **Being overweight** increases how much uric acid your body produces and the chance of it building up in your joints in the form of crystals.
- **Medical conditions** like high blood pressure, diabetes, obesity, and heart and kidney disease.
- A family history of gout can increase the chance that you will develop it as well.

- **Being a man** increases your risk for gout as men produce more uric acid compared to women.
- **Certain medications** like aspirin and medications used to control hypertension can increase levels of uric acid in your system.

#### **Rheumatoid Arthritis**

Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation. The disease mainly affects your joints but can cause damage to other body parts and systems such as your skin, eyes, lungs, blood vessels, and heart. Rheumatoid arthritis affects the linings in your joints resulting in painful swelling, bone erosion, and joint deformity. Symptoms of rheumatoid arthritis include tender, swollen, or warm joints, joint stiffness, fatigue, and loss of appetite. Early symptoms tend to start in smaller joints such as the joints in your fingers, toes, and feet. As the disease progresses, symptoms can spread to other larger joints in your body.

Risk factors for rheumatoid arthritis include:

- Your gender. You're more likely to get rheumatoid arthritis if you're a woman.
- Carrying excess weight and being obese increase your chances of developing rheumatoid arthritis.
- Your age. Although rheumatoid arthritis can occur at any age, it occurs more commonly in middle aged adults.
- Being a smoker.
- Having a family history of rheumatoid arthritis.

# **Tendonitis**

Tendons are fibrous connective tissue that attach muscles to the bone. <sup>12</sup> Tendonitis is a condition in which swelling happens around a tendon and causes pain when being active. <sup>13</sup> The muscles of your foot, ankle, and leg are attached to the bone by tendons. Tendonitis is one of the most common causes of foot and ankle pain. Tendonitis can occur in different parts of the foot and ankle including the posterior (back of the ankle), medial (side along the big toe), lateral (side along the pinky toe), and dorsal (top of the foot). The main symptoms of tendonitis are pain and swelling of the affected area. Symptoms often worsen when you move or stretch the affected tendon. Rest will usually ease symptoms but will return once activity resumes.

Causes of tendonitis can include:

- Overuse is the most common cause of tendonitis. This can mean a tendon has been stretched too far and may have been pulled apart or torn. Sport injuries are often linked to tendonitis as well as walking or running more intensely or more often than usual.<sup>14</sup>
- An abnormal foot structure such as flat feet or high arches can cause certain muscles to be overused or cause you to be off balanced. This can put more stress on your tendons as you walk, leading to swelling and inflammation of your tendons.
- A foot or ankle injury can often cause tendonitis. Sudden, powerful motions like jumping or repetitive motions in sports activities can cause your tendons to become irritated. This can also happen when your foot constantly rubs against your shoe. Tendonitis caused by these kinds of injuries are typically located at the top of the foot or heel.
- **Medical conditions** that cause general inflammation such as gout, rheumatoid arthritis, and spondyloarthropathy can often lead to tendonitis, particularly Achilles and posterior tibial tendonitis.

## **Other Causes of Chronic Foot Pain**

# **Bone Spurs**

Bone spurs are hard, calcium deposits that develop on the edges of bone. They are more commonly found in your joints, where bones meet each other. They may also form along your spine. Bone spurs are most associated with osteoarthritis, due to joint damage. Sometimes bone spurs can go undetected for years and cause no visible or painful symptoms. Other times, bone spurs can be incredibly painful and cause loss of motion in your joints. Heel spurs (bone spurs that appear on the underside of the heel bone) are commonly associated with plantar fasciitis. They appear because of strain on foot muscles and the stretching of the plantar fascia. They are common among athletes who perform lots of running and jumping activities.

#### **Broken Foot**

A broken foot can be the cause of numerous incidents, a car accident, sports injury, serious fall, accidental misstep, or dance injury. A broken foot injury can range from broken bones or tiny fractures in the bones in varying severities. Treatment for a broken foot can include the use of a cast or even surgery. Symptoms of a broken foot include pain and tenderness, inability to bear weight on the affected foot, bruising, swelling, or deformity. Healing a broken foot takes time. Pain medications, proper nutrition, and plenty of bed rest are recommended for treating a broken foot.

#### **Current Treatments for Chronic Foot Pain**

Treating chronic foot pain starts by finding the underlying cause for the pain. Symptoms usually subside once the problem is treated. Reducing inflammation helps to greatly reduce pain associated with foot pain disorders. Anti-inflammatory drugs may be prescribed for several weeks to address painful inflammation symptoms. Additionally, many treatments can be done on your own at home. Home remedies usually consist of over-the-counter pain-relieving medications like acetaminophen, ibuprofen, and topical analgesics like gels and creams. Resting your feet and icing them throughout the day will help to relieve pressure and swelling. Massaging your feet will also help to relieve pressure and swelling while reducing tension, increasing stimulation, and soothing aching muscles. It's also important to be proactive about preventing further foot pain or damage by wearing comfortable shoes and limiting activities that put too much pressure on your feet.

#### Other Treatments for Chronic Foot Pain

# **Physical Therapy**

Physical therapy will teach you exercises and stretches that can be used to strengthen your lower leg muscles, which may in turn ease pressure off your Achilles tendon and plantar fascia. It will also help to improve flexibility in your joints, which can ease pain and tightness.

## **Steroid Injections**

For patients suffering from painful plantar fasciitis symptoms, steroid injections can be injected into the foot to reduce inflammation causing the pain. Steroid injections contain medicine made from a group of drugs called corticosteroids, also known as cortisone. Common versions of cortisone injections include Kenalog® (triamcinolone), Depo-Medrol® (methylprednisolone), and Celestone® (betamethasone).¹¹ Cortisone is a synthetic version of cortisol, a hormone produced naturally by your body. Cortisone injections are injected into the affected area where it helps to reduce inflammation and pain, remove fluid, or thin out scar tissue and adhesions. Steroid injections are a non-invasive treatment for chronic foot pain; however, the effects are not permanent. There are different strengths of cortisone injections, the strongest lasting anywhere from 1-9 months.

# Weight-Loss

If you're carrying excess weight, you are putting more pressure on your feet. Reducing your weight will relieve some of this pressure and help ease painful symptoms. Obesity is also linked to diabetes, a common cause of foot pain from diabetic neuropathy. Losing weight can help to both reverse and prevent you from getting diabetes.

#### **Nerve Pain Medication**

Patients with severe chronic foot pain may be prescribed nerve pain medications or nerve block injections to numb the foot and stop the pain. Often medications used for epilepsy and depression are prescribed for nerve pain symptoms because of their effects on nerve signals. Anti-seizure medications like gabapentin (Neurontin®), carbamazepine (Tegretol®), and pregabalin (Lyrica®) are usually the first choice of treatment for neuropathic patients. However, anti-seizure, or anticonvulsant medications, can cause serious side effects like chest pain, heart problems, drowsiness, and nausea. Opioids are also sometimes used to treat nerve pain, though they are typically used as a last line of defense due to their potential for addiction and abuse. Some of these medications include oxycodone (OxyContin®), morphine, and tramadol (Ultram®).<sup>18</sup>

#### **Nutrition**

Many natural food sources contain essential vitamins and minerals that have been shown to help reduce inflammation and speed up the healing process. Eating a diet rich in these nutrient dense foods may help to relieve foot pain.

# **Chronic Foot Pain and Nutritional Supplements**

We're fortunate to live in an age where medications are readily available to treat a multitude of diseases and common health problems. However, medication alone does not always get to the root of the problem but acts merely as a Band-Aid to ease symptoms temporarily. Furthermore, medications carry the possibility of causing harmful or unwelcome side effects. While the role of nutrition is acknowledged in podiatry in pre and post foot surgery care, it's rarely considered as a preventative measure or treatment for chronic foot pain disorders. Nutrition plays a major role in our health. Vitamin deficiencies are associated with multiple health conditions, including inflammation and chronic foot pain disorders.

Unfortunately, Western diets rarely supply adequate levels of important vitamins and minerals that are essential to living a healthy, disease and pain free lifestyle. Our diets lack natural sources of important nutrients, and our behaviors (such as heavy drinking or smoking) can contribute to vitamin and mineral deficiency. Furthermore, vitamin deficiency can contribute to obesity, which is a common cause and contributor to foot pain.

## **Encouraging Lifestyle Changes Instead of Prescription Drugs**

A healthy lifestyle that includes regular exercise and a well-balanced diet is the best prevention against chronic foot pain disorders. It's estimated that more than 42.4% of adults in the United States are classified as obese. <sup>19</sup> Obesity is a common risk factor for type 2 diabetes, which is one of the leading causes of peripheral neuropathy. Obese individuals are also more at risk for

developing gout and suffering from plantar fasciitis pain. By making dietary changes, obese adults can reduce their weight and their risk of chronic foot pain disorders. A diet that consists of plenty of fruits and vegetables (especially leafy greens), whole-grain fiber, lean meats, poultry, fatty fish (like tuna and mackerel), and unsaturated fats (like avocados and nuts), is key to maintaining a healthy weight and adequate intake of nutrients. Natural, whole foods contain the necessary vitamins, minerals, and other nutrients the human body needs to function properly and fight off disease and inflammation.

When our body lacks these vital nutrients, health problems may arise which leads us to seek out medical advice. The use of nutrition and supplements is rarely advised as treatment for these health concerns, though in many cases, it may be a more effective and a safer treatment alternative. This White Paper aims to prove why natural ingredients in the form of dietary supplements may be a more proactive way to treat health problems, specifically chronic foot pain disorders. Supplements provide a safe and cost-effective way to treat vitamin and mineral deficiencies, without having to drastically change dietary or lifestyle habits. Numerous studies have been conducted on the role of nutrition for managing and treating health conditions that contribute to chronic foot pain. Specifically, the following 23 ingredients show the most promise in providing relief for sufferers of chronic foot pain disorders:

# Vitamin C (as Ascorbic Acid)

Most of us are familiar with Vitamin C for its role in strengthening the immune system. You may have found yourself drinking an extra glass of orange juice when you feel a cold coming on. Drinking a glass of orange juice may be just as helpful for treating pain associated with plantar fasciitis. Vitamin C, also called ascorbic acid, is an essential vitamin that plays an important role in regulating the immune system as well as in the production of collagen (the protein responsible for building bones, tendons, and ligaments). Vitamin C has antioxidant properties that help to reduce inflammation (which is caused by an immune response in the body) by neutralizing free radicals and protecting your cells from oxidative damage.<sup>20</sup>

Vitamin C may also provide some pain relief for symptoms of diabetic neuropathy. This essential vitamin has analgesic mechanisms that are likely due to its antioxidant and anti-inflammatory properties.<sup>21</sup> It's been shown to increase the synthesis of both catecholamine and dopamine and help in the synthesis of nor-epinephrine.<sup>22</sup> Catecholamine, dopamine, and nor-epinephrine are the neurotransmitters that help our body respond to stress or fright. They also play a significant role in pain relief.

You can get vitamin C in your diet through consuming foods such as citrus fruits, broccoli, tomatoes, and green peppers. Vitamin C can also be absorbed successfully when taken in supplement form. Because plantar fasciitis and chronic foot pain disorders are linked to inflammation, reducing inflammation by consuming more vitamin C may help to ease painful

symptoms. In addition, vitamin C seems to play a synergistic role in reducing pain in people with diabetic neuropathy. It's both a cost effective and easily obtainable remedy for pain relief.

## Vitamin D (as Cholecalciferol)

Vitamin D, or cholecalciferol (also called vitamin D3), is one of the few fat-soluble essential vitamins. You can get vitamin D through your diet by consuming foods like tuna, swordfish, cod liver oil, and juices and milks fortified with vitamin D. However, our main source of vitamin D comes from the sun. When UVB rays hit our skin, it interacts with cholesterol in our skin cells which stimulates the synthesis of vitamin D. Vitamin D is needed to maintain multiple bodily functions and for growing strong bones. This fat-soluble vitamin also plays a key role in maintaining the immune system by reducing inflammation.<sup>23-24</sup> In fact, several studies have shown a link between vitamin D deficiency and the presence of inflammation and disease caused by inflammation.<sup>25</sup>

In one study, patients with foot pain due to symptomatic knee osteoarthritis were found to have improvement in symptoms after vitamin D supplementation. <sup>26</sup> The study took 340 patients with symptomatic knee osteoarthritis and randomly prescribed them monthly treatments of either vitamin D3 or a placebo, over two years. Over the course of two years, foot pain worsened in patients who received the placebo and stayed the same or improved in patients given vitamin D3 supplementation. The study concluded that maintaining sufficient vitamin D levels can improve foot pain symptoms in those with knee osteoarthritis. Getting enough vitamin D through diet and sun exposure are the most effective ways of ensuring you do not become vitamin D deficient. However, supplementing with vitamin D3 in pill or capsule form has also been shown to be effective in improving vitamin deficiencies.

# Vitamin B12 (as Methylcobalamin)

Vitamin B12 is responsible for red blood cell production, regulating nerve function, and the production of DNA. It's found in animal products such as red meat, poultry, fish, and dairy. It can also be found in some fortified grain cereals. Vitamin B12 deficiency is not common in the United States but is more likely to occur in people who eat a vegan diet. Symptoms of B12 deficiency include weakness, lack of energy, anemia, mood disorders, and nerve damage.<sup>27</sup> B12 deficiency can also result in peripheral neuropathy, which is damage to the nerves outside the brain and spinal cord.<sup>28</sup> Neuropathy symptoms often manifest in the hands and feet as a tingling, "pins and needles" like sensation that can oftentimes be painful. Taking vitamin B12 supplements can help to improve deficiencies and treat deficiency symptoms, such as chronic foot pain caused by peripheral neuropathy. It's believed that B12 helps to relieve pain caused by neuropathy in several ways:<sup>29</sup>

• B12 helps to increase the regeneration of nerve tissue that's been damaged by misfiring nerves.

- It assists in the process of myelination, which is the process that creates protective sheaths over nerves in the body.
- It helps to reduce the firing of nerves associated with neuropathy.

Regular supplementation with B12 or B12 injections can be an effective way to combat painful symptoms of diabetic neuropathy induced foot pain.

# **Magnesium Bisglycinate Chelate**

Magnesium is an important mineral needed for over 300 enzyme systems and biochemical reactions in the body, including muscle and nerve function. It plays a role in nerve impulse conduction, regulating normal heart rhythm, and muscle contraction. Tood sources for magnesium include numerous plants, including green leafy vegetables, legumes, nuts, seeds, and whole grains. It's also found in fortified cereals and some brands of bottled water. A deficiency in magnesium can lead to potentially dangerous side effects. Early side effects of magnesium deficiency range from nausea, vomiting, weakness, and fatigue. Seriously low levels of magnesium can lead to numbness (most commonly in the hands and feet), tingling, cramps, seizures, muscle contractions, abnormal heart rhythm, and coronary spasms. Magnesium bisglycinate is an amino acid chelate that binds magnesium to glycine. In this lab created form, magnesium is more easily absorbed into the body by taking a supplement. Foot pain associated with magnesium deficiency may be treated through a magnesium rich diet and regular magnesium supplementation. Magnesium may help to reduce painful tingling sensations in the feet and relax muscle contractions associated with plantar fasciitis.

## Manganese Bisglycinate Chelate (as TRAACS®)

Manganese is a mineral found in foods such as nuts, tea, seeds, legumes, leafy greens, and whole grains. It is an essential nutrient needed for chemical bodily processes like processing cholesterol, carbohydrates, and protein. Manganese is needed for forming bone and cartilage as well. A deficiency in manganese can lead to weak or brittle bones. This trace mineral is also said to contain a powerful antioxidant called superoxide dismutase (SOD) that acts as an anti-inflammatory. SOD has been used as a therapeutic agent for inflammatory disorders.<sup>33</sup>

Osteoarthritis is a disease that causes the degeneration of the cartilage and underlying bone. It causes joint pain and stiffness, especially in the hips, knees, and thumbs. The critical driver of osteoarthritis is inflammation inside the joints. After 93 participants with osteoarthritis took a combination of manganese, glucosamine, and chondroitin supplement, 52% reported improvement in their symptoms after just 4 to 6 months.<sup>34</sup> Manganese supplementation helps address inflammation in the body, which in turn may help to ease chronic foot pain caused by inflamed foot tissue. Furthermore, manganese also helps to lower blood sugar. In fact, low levels

of manganese in the blood are common in those with diabetes.<sup>35</sup> Increasing manganese intake may help to reduce symptoms of chronic foot pain caused by diabetes.

# Zinc Glycinate Chelate (as TRAACS®)

Zinc is a micronutrient stored in small amounts throughout your body. We obtain zinc through our diet from foods such as red meat, poultry, and fortified grains. Zinc is necessary for a healthy functioning immune system, helping your body make DNA, supporting your sense of taste and smell, and aiding in wound healing. Zinc is commonly prescribed to help treat colds, cold sores, macular degeneration (an eye disease that leads to poor vision) and can also help to control blood sugar in individuals with diabetes. There is also some evidence to suggest that zinc can relieve painful symptoms of diabetic peripheral neuropathy by inhibiting oxidative stress.<sup>36</sup>

Nearly 30% of the elderly population in developed countries are zinc deficient. Chronic diseases that are often associated with the elderly (neuro-degenerative disorders, diabetes, atherosclerosis, Parkinson's disease, and macular degeneration) are linked to increased oxidative stress and chronic inflammation.<sup>37</sup> Zinc is an antioxidant and anti-inflammatory that has been shown to decrease incidence of infections, oxidative stress, and decrease the generation of inflammatory cytokines in the elderly when taken as a dietary supplement. Chelated zinc is a zinc supplement that is more easily absorbed by the body and may be more helpful for those who have a zinc deficiency.<sup>38</sup> Zinc may be beneficial for treating patients with chronic foot pain disorders by reducing inflammation and speeding up healing of foot pain caused by injury.

# Boswellia (Boswellia Serrata) Gum Resin Extract

Boswellia gum resin extract is taken from the Boswellia serrata tree, a plant native to India and some of Pakistan. The resin made from Boswellia tree extract has been used in Asian and African folk medicine for centuries. This herbal extract has been shown to provide anti-inflammatory benefits for a number of inflammatory illnesses and health conditions.<sup>39</sup> Boswellia's anti-inflammatory properties are due to Boswellia acid's ability to prevent the formation of leukotrienes, which are molecules in the body that are a cause of inflammation.<sup>40</sup> Some studies have shown that Boswellia may be helpful in treating osteoarthritis, rheumatoid arthritis, asthma, and inflammatory bowel disease. One study found that Boswellia helps to reduce joint swelling in those with rheumatoid arthritis.<sup>41</sup> It also acts as a powerful painkiller and can prevent the breakdown of cartilage.

## **White Willow Bark Extract**

Willow bark extract contains a chemical called salicin which acts as a natural analysic similar to aspirin. It's been used for thousands of years for its anti-inflammatory, antipyretic, and pain-relieving properties. Willow bark extract has been used to treat conditions such as osteoarthritis,

back pain, fever, flu, and muscle pain.<sup>42</sup> Willow bark also contains salicylates, polyphenols, and flavonoids, which have been shown to reduce pain and inflammation.<sup>43</sup> Adverse side effects to willow bark extract appear to be minimal in comparison to other pain-relieving medications, thus making it safer for long term use. It is also said to prevent the destruction of cartilage tissue.<sup>44</sup> Though willow bark generally has few negative side effects, because it contains the parent compound of aspirin, combining willow bark extract with NSAIDs (non-steroidal anti-inflammatory drugs) or corticosteroids is not recommended.

## **Bromelain**

Bromelain is a protein digesting enzyme that is derived from the core and stem of the pineapple fruit. It was first discovered in 1891 and then later made into supplement form in 1957. Bromelain has anti-inflammatory and analgesic properties that make it an effective treatment for the pain, swelling, and joint stiffness that is associated with osteoarthritis, plantar fasciitis, rheumatoid arthritis, and other chronic foot pain disorders. Studies have shown that Bromelain may be as effective for treating pain and inflammation associated with plantar fasciitis as ibuprofen or aspirin. Bromelain has also shown to be effective in accelerating healing and reducing bruising and swelling. Additionally, it can be used as a topical medication to remove dead skin from burns and orally to reduce soreness in aching muscles. Though eating pineapple whole may give you some of the benefits of bromelain, it's suggested to take bromelain in supplement form to get sufficient quantities of the beneficial enzymes.

## **Hvaluronic Acid (from Sodium Hvaluronate)**

Hyaluronic acid is a naturally occurring fluid found in the skin, joints, and eyes. The main activity of hyaluronic acid is to provide lubrication and keep your tissues hydrated. Artificial forms of hyaluronic acid can be created for use in dietary supplements and skincare products. One of the most common uses of hyaluronic acid is in treating symptoms of osteoarthritis. Hyaluronic acid injections can be used to relieve pain in the affected joints by providing moisture and reducing stiffness to the joints. Oral forms of hyaluronic acid have been shown to be beneficial as well. In a 2015 study, researchers found that a 3-month course of oral hyaluronic acid supplementation given to osteoarthritis patients, provided both a reduction in inflammation and an increase in the concentration of hyaluronic acid in joint fluids. Another study found that oral hyaluronic acid supplements lowered pain scores of osteoarthritis patients, improved sleep, and led to a reduced intake of pain medications. A 2008 study found that orally administered hyaluronic acid supplementation improved quality of life for sufferers of knee osteoarthritis. Hyaluronic acid has also been used to treat conditions such as erectile dysfunction, chronic fatigue syndrome, fibromyalgia, osteoporosis, skin wrinkles, and chronic pain.

# MSM (Methylsulfonylmethane)

Methylsulfonylmethane (MSM) is a sulfur-containing compound that is found naturally in humans, animals, and plants. Synthetic forms of MSM can also be created in laboratories for use as dietary supplements in powder or capsule form. The dietary supplement is widely used in alternative medicine for treating joint pain associated with arthritis, boosting immunity, and reducing inflammation. In addition to providing significant anti-inflammatory benefits, studies have shown that MSM also inhibits the breakdown of cartilage.<sup>49</sup> Other studies show that MSM can help to reduce muscle and joint pain as well as stiffness and swelling in the joints.<sup>50</sup> MSM's potent anti-inflammatory properties are attributed to its ability to inhibit a protein complex called NF-kB and cytokines, which are known causes of producing inflammation in the body. <sup>51,52</sup>

# **Hydrolyzed Collagen**

Hydrolyzed collagen is collagen that has been broken down into smaller, easy to process particles that are more easily absorbed in the body. Collagen is a protein found naturally in humans and animals that is responsible for making connective tissue, like skin, cartilage, tendons, organs, and bones. Hydrolyzed collagen is taken in supplement form to provide benefits for skin health, promote hair and nail growth, and relieve joint pain. Studies have shown that collagen supplementation can help to strengthen joints and reduce pain associated with osteoarthritis.<sup>53</sup> As the body ages, we naturally lose collagen. The loss of collagen can result in the loss of cartilage, the tissue that protects our joints. By increasing our levels of collagen, we may be able to preserve cartilage and bone mass.

#### Curcumin

Curcumin is the main compound in the popular spice turmeric, a fragrant, yellow ingredient used in many Asian dishes. Curcumin is widely known for its anti-inflammatory properties that help in treating conditions such as arthritis, hyperlipidemia, and exercise induced inflammation and muscle soreness.<sup>54</sup> In one study, curcumin was shown to provide even greater anti-inflammatory effects on patients with rheumatoid arthritis than other leading anti-inflammatory drugs. It also seems to lessen some of the symptoms associated with rheumatoid arthritis, such as morning stiffness and joint swelling, and tendonitis.<sup>55</sup> The anti-inflammatory effects of curcumin may be due to its ability to control cytokines, which are proteins in the body responsible for causing inflammation.<sup>56</sup> Curcumin is also an antioxidant that fights free radicals in the body that can cause cancers.

#### **Bioperine**

Piperine (also known as black pepper) is an alkaloid, a plant compound like capsaicin, the active ingredient in cayenne pepper. Piperine may help to relieve poor digestion, nausea, and headaches. It's also been shown to have anti-inflammatory properties. Most importantly, piperine has a unique ability to boost the absorption of curcumin.<sup>57</sup> Curcumin has powerful anti-inflammatory benefits on our health but is unfortunately poorly absorbed by the body for use.

However, combining piperine with curcumin enhances absorption by up to 2,000 percent.<sup>58</sup> Piperine may help curcumin pass through the intestinal wall more easily therefore allowing it to reach the bloodstream faster.<sup>59</sup> It may also slow down the breakdown of curcumin by the liver, increasing its blood levels.<sup>60</sup> Bioperine is a piperine extract that contains at least 95% piperine.<sup>61</sup> It's made to be more easily absorbed by the body for maximum health benefits.

## **Silica**

Silica, also known as silicon dioxide (SiO2), is a natural trace mineral made from the combination of silicon and oxygen. It's found in foods such as leafy greens and whole grains as well as in the form of supplements and extracts. Silicon is important for building and maintaining strong bones. The trace mineral supports the formation of collagen fibers, which is the essential protein needed for building bone and cartilage. According to one study, silica also stimulates the growth of bone cells, called osteoblasts. <sup>62</sup> In addition, silica inhibits the production of cells that break down your bones, called osteoclasts. <sup>63</sup> Increased bone mass density and bone strength can reduce risk of osteoporosis, a degenerative disease that breaks down bone tissue. Silica may in turn help to reduce the likelihood of developing chronic foot pain from degenerative diseases.

#### **L-Proline**

L-proline is an amino acid found naturally within the human body. Even though we produce it on our own, we also get L-proline from our diet from protein-rich foods like meat, fish, and dairy. The body uses proline to make proteins, such as collagen. In supplement form, proline is usually taken to support joint and skin health as well as aid in muscle and injury recovery. <sup>64</sup> A low protein diet, chronic injuries, and some illnesses may inhibit your body from making adequate amounts of L-proline. Endurance athletes, such as long-distance runners, may also be at risk for L-proline deficiency. Signs of proline deficiency include wrinkles and sores that are slow healing and chronic joint pain due to degenerating cartilage tissue. Eating a protein-rich diet and supplementing with L-proline can help to restore levels of proline in the body and repair damaged tissues.

## L-Glutamine

L-glutamine is an amino acid important for many biological processes, including the synthesis of protein, regulating the immune system, and maintaining and repairing intestinal tissues. L-glutamine is produced in the muscles but can also be obtained through diet from foods, such as

chicken, fish, dairy, lentils, spinach, and cabbage. Supplementation of glutamine is commonly used to aid in recovery from trauma or injury. L-glutamine can help by stimulating protein synthesis and the immune function to better help the body heal from trauma or surgeries. Some research has shown that L-glutamine may also help with treating chemotherapy induced peripheral neuropathy. This is speculated to be caused by L-glutamine playing a neuroprotective role due to the upregulation of nerve growth factor. Oral glutamine supplementation was shown to be effective in reducing peripheral neuropathy symptoms such as numbness, motor weakness, dysesthesias, and loss of vibratory sensation.

# **Glucosamine (as Glucosamine Sulfate Complex)**

Glucosamine is an amino sugar that occurs naturally in your body. Its main role is in helping your body to build cartilage, tendons, ligaments, and the fluid that surrounds your joints. Glucosamine does not occur naturally in foods. The only other place it's found is in shellfish shells, animal bones, and fungi. His from these sources that glucosamine supplements are often made. Glucosamine supplements have been used to increase the cartilage and fluid around the joints to help prevent and ease symptoms of joint disorders like osteoarthritis. In combination with chondroitin sulfate, glucosamine also helps to reduce inflammation. In one study of 18 overweight adults, daily glucosamine and chondroitin sulfate supplementation reduced inflammation markers by 23% compared to a placebo. Glucosamine has been shown to have unique anti-inflammatory effects similar to non-steroidal anti-inflammatory drugs (NSAIDs). In some laboratory tests, glucosamine supplements demonstrated a protective effect on cartilage. This suggests that glucosamine may reduce the breakdown of cartilage that occurs in patients with osteoarthritis. Additionally, glucosamine's anti-inflammatory effects have also been associated with a lower risk of type 2 diabetes.

#### **Chondroitin Sulfate**

Chondroitin sulfate is a naturally occurring compound in the human body that is essential for building cartilage tissue. It's also present in certain animal-based foods like bone broth, stews, and soups that contain meats with connective tissues. In supplement form, it is often combined with glucosamine to help treat osteoarthritis.<sup>71</sup> Studies show that chondroitin and glucosamine can improve joint function and relieve pain symptoms in people with osteoarthritis.<sup>72</sup> Chondroitin has similar anti-inflammatory properties to glucosamine sulfate. It may also help to slow the breakdown of cartilage and joint damage in those who suffer from osteoarthritis. Chondroitin sulfate in supplement form is considered safe for long term use and has relatively few, mild side effects.

## L-Arginine

L- arginine is an amino acid necessary for making proteins in the body and is important for regulating blood circulation. L-arginine is found naturally in meat and dairy products like

turkey, red meats, and cheese. Your body converts L-arginine into nitric oxide, which causes your blood vessels to widen for better blood flow.<sup>73</sup> People use L-arginine as a supplement for chest pain, blood flow issues, high blood pressure during pregnancy, and erectile dysfunction. It's also known for boosting the immune system, helping the kidneys clear waste, and aiding in wound repair. L-arginine may help relieve leg and foot pain in those suffering from diabetic neuropathy. In one animal study, researchers found that L-arginine supplementation reduced pain in rats with diabetic neuropathy after just 3-weeks.<sup>74</sup> This effect could be due to L-arginine's ability to open small blood vessels in the body and increase blood flow to damaged nerves.

# Alpha Lipoic Acid

Alpha-lipoic acid (ALA) is an antioxidant that is made naturally by the body and can be found in some foods such as broccoli, spinach, red meats, and carrots. It's been shown to exhibit multiple health benefits such as anti-inflammatory, anti-cancer, anti-microbial, and anti-diabetic properties. ALA's primary function is to help break down carbohydrates in the body for use as energy, though it has also been shown to be beneficial for treating diabetic nerve pain. The powerful antioxidant properties of ALA prevent and repair damage done to cells because of oxidative stress. Oxidative stress caused by hyperglycemia specifically damages nerve cells, thus leading to neuropathy in diabetics. ALA has been shown to reduce painful symptoms of diabetic neuropathy, including pain, tingling, and prickling in the feet and legs. Chronic foot pain disorders due to nerve damage or inflammation may benefit from ALA's powerful antioxidant effects.

#### **Benfotiamine**

Benfotiamine is the synthetic variant of thiamine, also known as vitamin B1. Vitamin B1 is found naturally in foods such as legumes, nuts, and fortified grain products like cereals, pasta, and rice. Benfotiamine is fat soluble rather than water soluble (like most vitamins), allowing for better absorption in the body than naturally occurring vitamin B1 from food sources. Low levels of thiamine have been linked to diseases such as Alzheimer's disease and diabetes. Research has shown that benfotiamine is helpful in easing symptoms of nerve damage or neuropathy caused by diabetes. It does so by helping to reduce free radical damage and prevent dangerous side effects from too much sugar in the bloodstream. Benfotiamine promotes blood vessel health by improving circulation which can sometimes be impacted by neuropathy. Benfotiamine supplementation can restore thiamine levels in the body and prevent or treat nerve damage in the feet and legs caused by diabetic neuropathy.

# **Acetyl L-Carnitine**

Acetyl L-carnitine is made from the amino acid L-carnitine, which is found in red meat. The body uses L-carnitine in small amounts in the brain, kidneys, and liver. The amino acid is used

by the body to turn fat into energy. Acetyl L-carnitine is used for treating Alzheimer's disease, depression, improving memory and thinking skills, and treating nerve pain in those with neuropathy. In recent years, acetyl L-carnitine has gained growing clinical interest for its analgesic effect in treating painful symptoms of neuropathy as well as pain prevention.<sup>79</sup> Animal studies have shown that acetyl L-carnitine provides a neuroprotective function in subjects with diabetic neuropathy, thus helping to relieve painful symptoms and improve nerve fiber regeneration.

# **Supplement Safety**

Nutritional supplements have the potential to treat foot pain disorders, improve painful symptoms of inflammation, improve overall health and reduce the risk of other serious illnesses and diseases. There is enough evidence to suggest that nutritional therapy can be just as beneficial in treating common foot pain disorders as prescription drugs or other therapies. Nutritional therapy provides a cost-effective, safe alternative to other methods of treatment with low risk for complications or adverse effects. It must be noted, however, that not all supplements are created equal. When utilizing supplements for clinical use, correct dosages must be administered while avoiding interactions with other medications. It's also important to choose supplements made from only high grade, responsibly sourced, and verified ingredients.

Unfortunately, the standards for the supplement market are not enforced by the Food and Drug Administration (FDA), leaving room for variable supplement quality. When choosing supplement products for treatment of specific ailments, consumers are urged to do their own research. Many supplement product companies will make false claims about the purity and quality of their ingredients, as well as their benefits. For this reason, consumers should only buy from companies that produce their products in FDA registered facilities that use Good Manufacturing Practice (GMP) standards and undergo third-party lab testing. Evidence of these quality control measures should be posted somewhere on their company website in the form of a verified badge.

# PodiVite<sup>TM</sup> for Chronic Foot Pain

Treating chronic foot pain should be approached from multiple avenues. Certainly, finding the root cause of chronic foot pain is paramount to discerning the correct form of treatment. In many cases, treating the cause of chronic foot pain relieves the problem altogether. However, in cases where the cause of pain is unknown, treatment consists of managing and relieving symptoms that cause patients' discomfort. Vitamin deficiency is an often-overlooked cause of and treatment for numerous health conditions, like chronic foot pain disorders. There are also natural ingredients often used in alternative medicine that have been proven to be beneficial in providing pain relief and anti-inflammatory effects. The 23 different vitamins, minerals, natural herbs, and supplements outlined in this document are proof of alternative remedies for chronic

foot pain. PodiVite, a product by Zen Nutrients, is a high potency nutraceutical specifically formulated with these 23 ingredients to provide the first daily natural solution to chronic foot pain.

PodiVite was created as an alternative treatment to prescription drugs and pain relievers that are often prescribed for foot and ankle pain. While effective, these drugs can have harmful side effects on some patients or not be safe for long-term use. Furthermore, certain prescription medicines have the possibility of becoming habit forming. PodiVite was created by a team of experienced physicians and pharmacists, with the goal of providing a natural treatment for foot related pain disorders. All 23 ingredients in PodiVite are pharmaceutical-grade and backed by science for their effectiveness in treating chronic foot pain disorders such as plantar fasciitis, tendonitis, peripheral neuropathy, and more. In addition, PodiVite, as all of Zen Nutrient's supplement products, is formulated in an FDA registered lab and has been subject to third party testing for safety and efficacy. Natural supplements provide a healthy, non-addictive, safer and less expensive method for treating chronic pain.

## **Conclusion**

The purpose of this White Paper was to address the beneficial outcome of nutritional supplements for treating symptoms of plantar fasciitis and other chronic foot pain disorders. There is clear scientific evidence to back up these claims. Nutritional supplementation is underutilized in the healthcare industry, though it could prove to be a more effective and safe way to treat chronic pain. By combining the 23 most effective nutritional supplements for chronic foot pain, PodiVite is the first daily supplement to offer natural, non-habit-forming relief. By following Good Manufacturing Practice standards and ensuring verifiable quality control, PodiVite stands out as an effective nutraceutical consumers can trust.

## References

- 1. New Survey Reveals Majority of Americans Suffer from Foot Pain. (2014, May 19). PR Newswire. Retrieved January 24, 2022, from <a href="https://www.prnewswire.com/news-releases/new-survey-reveals-majority-of-americans-suffer-from-foot-pain-259775741.html">https://www.prnewswire.com/news-releases/new-survey-reveals-majority-of-americans-suffer-from-foot-pain-259775741.html</a>
- 2. Inflammation: What Is It, Causes, Symptoms & Treatment. (2021, July 28). Cleveland Clinic. Retrieved January 22, 2022, from <a href="https://my.clevelandclinic.org/health/symptoms/21660-inflammation">https://my.clevelandclinic.org/health/symptoms/21660-inflammation</a>
- 3. Zhang, J. M., & An, J. (2007). Cytokines, inflammation, and pain. *International anesthesiology clinics*, 45(2), 27–37. https://doi.org/10.1097/AIA.ob013e318034194e
- 4. Sampson, S. (n.d.). *Autoimmune Diseases: Types, Symptoms, Causes & More*. Healthline. Retrieved January 22, 2022, from <a href="https://www.healthline.com/health/autoimmune-disorders">https://www.healthline.com/health/autoimmune-disorders</a>
- 5. Inflammation: What Is It, Causes, Symptoms & Treatment. (2021, July 28). Cleveland Clinic. Retrieved January 22, 2022, from <a href="https://my.clevelandclinic.org/health/symptoms/21660-inflammation">https://my.clevelandclinic.org/health/symptoms/21660-inflammation</a>
- 6. Plantar fasciitis Symptoms and causes. (n.d.). Mayo Clinic. Retrieved January 22, 2022, from <a href="https://www.mayoclinic.org/diseases-conditions/plantar-fasciitis/symptoms-causes/syc-20354846">https://www.mayoclinic.org/diseases-conditions/plantar-fasciitis/symptoms-causes/syc-20354846</a>
- 7. Ihli, N., & Langdon, K. (n.d.). *Heel Pain in Older Adults and the Elderly*. Heel That Pain. Retrieved January 22, 2022, from <a href="https://heelthatpain.com/heel-pain/elderly/">https://heelthatpain.com/heel-pain/elderly/</a>
- 8. Peripheral neuropathy Symptoms and causes. (2021, July 3). Mayo Clinic. Retrieved January 22, 2022, from <a href="https://www.mayoclinic.org/diseases-conditions/peripheral-neuropathy/symptoms-causes/syc-20352061">https://www.mayoclinic.org/diseases-conditions/peripheral-neuropathy/symptoms-causes/syc-20352061</a>
- 9. Gout Symptoms and causes. (2021, March 6). Mayo Clinic. Retrieved January 22, 2022, from <a href="https://www.mayoclinic.org/diseases-conditions/gout/symptoms-causes/syc-20372897">https://www.mayoclinic.org/diseases-conditions/gout/symptoms-causes/syc-20372897</a>
- 10. Frank, J. (n.d.). *What Are Purines?* Arthritis-health. Retrieved January 22, 2022, from https://www.arthritis-health.com/types/gout/what-are-purines

- 11. *Rheumatoid arthritis Symptoms and causes*. (2021, May 18). Mayo Clinic. Retrieved January 22, 2022, from <a href="https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/symptoms-causes/syc-20353648">https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/symptoms-causes/syc-20353648</a>
- 12. *Tendon vs. ligament*. (2020, August 13). MedlinePlus. Retrieved January 22, 2022, from <a href="https://medlineplus.gov/ency/imagepages/19089.htm">https://medlineplus.gov/ency/imagepages/19089.htm</a>
- 13. Kaux JF, Forthomme B, Goff CL, Crielaard JM, Croisier JL. <u>Current opinions on tendinopathy</u>. *J Sports Sci Med*. 2011;10(2):238-53.
- 14. Houghton KM. <u>Review for the generalist: evaluation of pediatric foot and ankle pain.</u> *Pediatr Rheumatol Online J.* 2008;6:6. doi:10.1186/1546-0096-6-6
- 15. Bone spurs Symptoms and causes. (2019, October 17). Mayo Clinic. Retrieved January 22, 2022, from <a href="https://www.mayoclinic.org/diseases-conditions/bone-spurs/symptoms-causes/syc-20370212">https://www.mayoclinic.org/diseases-conditions/bone-spurs/symptoms-causes/syc-20370212</a>
- 16. *Plantar fasciitis Diagnosis and treatment*. (2022, January 20). Mayo Clinic. Retrieved January 22, 2022, from <a href="https://www.mayoclinic.org/diseases-conditions/plantar-fasciitis/diagnosis-treatment/drc-20354851">https://www.mayoclinic.org/diseases-conditions/plantar-fasciitis/diagnosis-treatment/drc-20354851</a>
- 17. *Cortisone Shots: Treatment, Side Effects, Outlook.* (2018, April 10). Cleveland Clinic. Retrieved January 24, 2022, from <a href="https://my.clevelandclinic.org/health/treatments/17759-cortisone-shots">https://my.clevelandclinic.org/health/treatments/17759-cortisone-shots</a>
- 18. Sein, M. (n.d.). *Medications for Neuropathic Pain*. Spine-health. Retrieved January 24, 2022, from <a href="https://www.spine-health.com/treatment/pain-management/medications-neuropathic-pain">https://www.spine-health.com/treatment/pain-management/medications-neuropathic-pain</a>
- 19. *Adult Obesity Facts* | *Overweight & Obesity*. (n.d.). CDC. Retrieved January 22, 2022, from <a href="https://www.cdc.gov/obesity/data/adult.html">https://www.cdc.gov/obesity/data/adult.html</a>
- 20. Carr, A. C., & Maggini, S. (2017). Vitamin C and Immune Function. *Nutrients*, *9*(11), 1211. <a href="https://doi.org/10.3390/nu9111211">https://doi.org/10.3390/nu9111211</a>
- 21. Carr AC, McCall C: The role of vitamin C in the treatment of pain: new insights. J Transl Med. 2017, 15:77. 10.1186/s12967-017-1179-7
- 22. Chaitanya NC, Muthukrishnan A, Krishnaprasad CMS, Sanjuprasanna G, Pillay P, Mounika B: An insight and update on the analgesic properties of vitamin C. J Pharm Bioallied Sci. 2018, 10:119-25. 10.4103/jpbs.JPBS\_12\_18
- 23. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.

- 24. Norman AW, Henry HH. Vitamin D. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition, 10th ed. Washington DC: Wiley-Blackwell, 2012.
- 25. Jones G. Vitamin D. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. Modern Nutrition in Health and Disease, 11th ed. Philadelphia: Lippincott Williams & Wilkins, 2014.
- 26. Querfeld U. (2013). Vitamin D and inflammation. *Pediatric nephrology (Berlin, Germany)*, 28(4), 605–610. <a href="https://doi.org/10.1007/s00467-012-2377-4">https://doi.org/10.1007/s00467-012-2377-4</a>
- 27. Tu L, Zheng S, Cicuttini F, et al. <u>Effects of vitamin D supplementation on disabling foot pain in patients with symptomatic knee osteoarthritis</u> [published online Jul 5, 2020]. *Arthritis Care Res (Hoboken)*. doi:10.1002/acr.24371
- 28. *Vitamin B-12*. (n.d.). Mayo Clinic. Retrieved January 22, 2022, from <a href="https://www.mayoclinic.org/drugs-supplements-vitamin-b12/art-20363663">https://www.mayoclinic.org/drugs-supplements-vitamin-b12/art-20363663</a>
- 29. *Peripheral Neuropathy Caused by Vitamin B12 Deficiency*. (n.d.). Practical Neurology. Retrieved January 22, 2022, from <a href="https://practicalneurology.com/articles/2020-mar/peripheral-neuropathy-caused-by-vitamin-b12-deficiency">https://practicalneurology.com/articles/2020-mar/peripheral-neuropathy-caused-by-vitamin-b12-deficiency</a>
- 30. *Vitamin B12 Ideal Foot & Ankle Group*. (n.d.). Astoria Podiatrist | Foot Doctor in Astoria. Retrieved January 22, 2022, from <a href="https://www.idealpodiatry.com/vitamin-b12/">https://www.idealpodiatry.com/vitamin-b12/</a>
- 31. Institute of Medicine (IOM). Food and Nutrition Board. <u>Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride</u>. Washington, DC: National Academy Press, 1997.
- 32. Rude RK. Magnesium. In: Coates PM, Betz JM, Blackman MR, Cragg GM, Levine M, Moss J, White JD, eds. Encyclopedia of Dietary Supplements. 2nd ed. New York, NY: Informa Healthcare; 2010:527-37.
- 33. Rude RK. Magnesium. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. Modern Nutrition in Health and Disease. 11th ed. Baltimore, Mass: Lippincott Williams & Wilkins; 2012:159-75.
- 34. Yasui, K., & Baba, A. (2006). Therapeutic potential of superoxide dismutase (SOD) for resolution of inflammation. *Inflammation research : official journal of the European Histamine Research Society ...* [et al.], 55(9), 359–363. https://doi.org/10.1007/s00011-006-5195-y
- 35. Das, A., Jr, & Hammad, T. A. (2000). Efficacy of a combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. *Osteoarthritis and cartilage*, *8*(5), 343–350. <a href="https://doi.org/10.1053/joca.1999.0308">https://doi.org/10.1053/joca.1999.0308</a>

- 36. Koh, E. S., Kim, S. J., Yoon, H. E., Chung, J. H., Chung, S., Park, C. W., Chang, Y. S., & Shin, S. J. (2014). Association of blood manganese level with diabetes and renal dysfunction: a cross-sectional study of the Korean general population. *BMC endocrine disorders*, *14*, 24. <a href="https://doi.org/10.1186/1472-6823-14-24">https://doi.org/10.1186/1472-6823-14-24</a>
- 37. Liu, F., Ma, F., Kong, G., Wu, K., Deng, Z., & Wang, H. (2014). Zinc supplementation alleviates diabetic peripheral neuropathy by inhibiting oxidative stress and upregulating metallothionein in peripheral nerves of diabetic rats. *Biological trace element research*, *158*(2), 211–218. <a href="https://doi.org/10.1007/s12011-014-9923-9">https://doi.org/10.1007/s12011-014-9923-9</a>
- 38. Prasad A. S. (2014). Zinc: an antioxidant and anti-inflammatory agent: role of zinc in degenerative disorders of aging. *Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS)*, 28(4), 364–371. https://doi.org/10.1016/j.jtemb.2014.07.019
- 39. *Chelated Zinc: Benefits, Types, and Best Absorption*. (2019, December 3). Healthline. Retrieved January 22, 2022, from <a href="https://www.healthline.com/health/chelated-zinc">https://www.healthline.com/health/chelated-zinc</a>
- 40. *Boswellia: Uses, Dosage, Side Effects, and More*. (n.d.). Healthline. Retrieved January 22, 2022, from <a href="https://www.healthline.com/health/boswellia">https://www.healthline.com/health/boswellia</a>
- 41. S. Singh, A. Khajuria, S.C. Taneja, R.K. Johri, J. Singh, G.N. Qazi, *Boswellic acids: A leukotriene inhibitor also effective through topical application in inflammatory disorders*, Phytomedicine, Volume 15, Issues 6–7,2008, Pages 400-407, ISSN 0944-7113, https://doi.org/10.1016/j.phymed.2007.11.019. (https://www.sciencedirect.com/science/article/pii/S0944711307002917)
- 42. WILLOW BARK: Overview, Uses, Side Effects, Precautions, Interactions, Dosing and Reviews. (n.d.). WebMD. Retrieved January 22, 2022, from <a href="https://www.webmd.com/vitamins/ai/ingredientmono-955/willow-bark">https://www.webmd.com/vitamins/ai/ingredientmono-955/willow-bark</a>
- 43. Shara, M., & Stohs, S. J. (2015). Efficacy and Safety of White Willow Bark (Salix alba) Extracts. *Phytotherapy research*: *PTR*, 29(8), 1112–1116. https://doi.org/10.1002/ptr.5377
- 44. Altshul, S. (2011, November 3). *Willow Bark For Backache*. Prevention.com. Retrieved January 22, 2022, from <a href="https://www.prevention.com/health/a20436719/willow-bark-for-backache/">https://www.prevention.com/health/a20436719/willow-bark-for-backache/</a>
- 45. Brien, S., Lewith, G., Walker, A., Hicks, S. M., & Middleton, D. (2004). Bromelain as a Treatment for Osteoarthritis: a Review of Clinical Studies. *Evidence-based complementary and alternative medicine*: eCAM, 1(3), 251–257. https://doi.org/10.1093/ecam/neh035
- 46. Nelson FR, Zvirbulis RA, Zonca B, et al. <u>The effects of an oral preparation containing hyaluronic acid (Oralvisc®) on obese knee osteoarthritis patients determined by pain, function, bradykinin, leptin, inflammatory cytokines, and heavy water analyses. *Rheumatol Int.* 2015 Jan;35(1):43-52. doi:10.1007/s00296-014-3047-6</u>

- 47. Jensen GS, Attridge VL, Lenninger MR, Benson KF. <u>Oral intake of a liquid high-molecular-weight hyaluronan associated with relief of chronic pain and reduced use of pain medication: results of a randomized, placebo-controlled double-blind pilot study. *J Med Food.* 2015 Jan;18(1):95-101. doi:10.1089/jmf.2013.017</u>
- 48. Kalman, D.S., Heimer, M., Valdeon, A. *et al.* Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint®) on pain relief and quality of life in subjects with knee osteoarthritis: a pilot randomized double-blind placebo-controlled trial. *Nutr J* 7, 3 (2008). <a href="https://doi.org/10.1186/1475-2891-7-3">https://doi.org/10.1186/1475-2891-7-3</a>
- 49. Ezaki, J., Hashimoto, M., Hosokawa, Y., & Ishimi, Y. (2013). Assessment of safety and efficacy of methylsulfonylmethane on bone and knee joints in osteoarthritis animal model. *Journal of bone and mineral metabolism*, *31*(1), 16–25. <a href="https://doi.org/10.1007/s00774-012-0378-9">https://doi.org/10.1007/s00774-012-0378-9</a>
- 50. Xu, G., Zhou, T., Gu, Y., Wang, Q., Shariff, M., Gu, P., Nguyen, T., Shi, R., & Rao, J. (2015). Evaluation of the Effect of Mega MSM on Improving Joint Function in Populations Experiencing Joint Degeneration. *International journal of biomedical science : IJBS*, 11(2), 54–60.
- 51. Lawrence T. (2009). The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harbor perspectives in biology*, 1(6), a001651. <a href="https://doi.org/10.1101/cshperspect.a001651">https://doi.org/10.1101/cshperspect.a001651</a>
- 52. Ahn, H., Kim, J., Lee, M. J., Kim, Y. J., Cho, Y. W., & Lee, G. S. (2015). Methylsulfonylmethane inhibits NLRP3 inflammasome activation. *Cytokine*, 71(2), 223–231. https://doi.org/10.1016/j.cyto.2014.11.001
- 53. Kilinc, B. E., Oc, Y., Alibakan, G., Bilgin, E., Kanar, M., & Eren, O. T. (2018). An Observational 1-Month Trial on the Efficacy and Safety of Promerim for Improving Knee Joint. *Clinical medicine insights. Arthritis and musculoskeletal disorders*, *11*, 1179544118757496. https://doi.org/10.1177/1179544118757496
- 54. Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: A Review of Its Effects on Human Health. *Foods (Basel, Switzerland)*, 6(10), 92. <a href="https://doi.org/10.3390/foods6100092">https://doi.org/10.3390/foods6100092</a>
- 55. Chandran, B., & Goel, A. (2012). A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytotherapy research: PTR*, *26*(11), 1719–1725. <a href="https://doi.org/10.1002/ptr.4639">https://doi.org/10.1002/ptr.4639</a>
- 56. Hasriadi, Dasuni Wasana PW, Vajragupta O, Rojsitthisak P, Towiwat P. <u>Mechanistic insight into the effects of curcumin on neuroinflammation-driven chronic pain</u>. *Pharmaceuticals*. 2021;14(8):777. doi:10.3390%2Fph14080777
- 57. Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., & Srinivas, P. S. (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta medica*, 64(4), 353–356. https://doi.org/10.1055/s-2006-957450

- 58. Prasad, S., Tyagi, A. K., & Aggarwal, B. B. (2014). Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. *Cancer research and treatment*, *46*(1), 2–18. https://doi.org/10.4143/crt.2014.46.1.2
- 59. Kesarwani, K., Gupta, R., & Mukerjee, A. (2013). Bioavailability enhancers of herbal origin: an overview. *Asian Pacific journal of tropical biomedicine*, *3*(4), 253–266. https://doi.org/10.1016/S2221-1691(13)60060-X
- 60. Singh, J., Dubey, R. K., & Atal, C. K. (1986). Piperine-mediated inhibition of glucuronidation activity in isolated epithelial cells of the guinea-pig small intestine: evidence that piperine lowers the endogeneous UDP-glucuronic acid content. *The Journal of pharmacology and experimental therapeutics*, *236*(2), 488–493.
- 61. Meixner, M. (2021, September 1). 5 Emerging Benefits of BioPerine and Piperine Supplements. Healthline. Retrieved January 24, 2022, from <a href="https://www.healthline.com/nutrition/bioperine-and-piperine-supplement-benefits">https://www.healthline.com/nutrition/bioperine-and-piperine-supplement-benefits</a>
- 62. Reffitt, D. M., Ogston, N., Jugdaohsingh, R., Cheung, H. F., Evans, B. A., Thompson, R. P., Powell, J. J., & Hampson, G. N. (2003). Orthosilicic acid stimulates collagen type 1 synthesis and osteoblastic differentiation in human osteoblast-like cells in vitro. *Bone*, *32*(2), 127–135. https://doi.org/10.1016/s8756-3282(02)00950-x
- 63. Mladenović, Ž., Johansson, A., Willman, B., Shahabi, K., Björn, E., & Ransjö, M. (2014). Soluble silica inhibits osteoclast formation and bone resorption in vitro. *Acta biomaterialia*, 10(1), 406–418. <a href="https://doi.org/10.1016/j.actbio.2013.08.039">https://doi.org/10.1016/j.actbio.2013.08.039</a>
- 64. Wu, G., Bazer, F. W., Burghardt, R. C., Johnson, G. A., Kim, S. W., Knabe, D. A., Li, P., Li, X., McKnight, J. R., Satterfield, M. C., & Spencer, T. E. (2011). Proline and hydroxyproline metabolism: implications for animal and human nutrition. *Amino acids*, *40*(4), 1053–1063. <a href="https://doi.org/10.1007/s00726-010-0715-z">https://doi.org/10.1007/s00726-010-0715-z</a>
- 65. Miller AL. <u>Therapeutic considerations of L-glutamine: a review of the literature</u>. Altern Med Rev. 1999;4(4):239-48.
- 66. Amara S. (2008). Oral glutamine for the prevention of chemotherapy-induced peripheral neuropathy. *The Annals of pharmacotherapy*, *42*(10), 1481–1485. <a href="https://doi.org/10.1345/aph.1L179">https://doi.org/10.1345/aph.1L179</a>
- 67. *Glucosamine*. (n.d.). MedlinePlus. Retrieved January 22, 2022, from <a href="https://medlineplus.gov/druginfo/natural/807.html">https://medlineplus.gov/druginfo/natural/807.html</a>
- 68. Spiridakis, N. (2021, October 6). *Are There Any Foods That Contain Glucosamine?* Livestrong.com. Retrieved January 22, 2022, from <a href="https://www.livestrong.com/article/203234-what-foods-have-glucosamine/">https://www.livestrong.com/article/203234-what-foods-have-glucosamine/</a>

- 69. Navarro, S. L., White, E., Kantor, E. D., Zhang, Y., Rho, J., Song, X., Milne, G. L., Lampe, P. D., & Lampe, J. W. (2015). Randomized trial of glucosamine and chondroitin supplementation on inflammation and oxidative stress biomarkers and plasma proteomics profiles in healthy humans. *PloS one*, 10(2), e0117534. https://doi.org/10.1371/journal.pone.0117534
- 70. Ma, H., Li, X., Zhou, T., Sun, D., Liang, Z., Li, Y., Heianza, Y., & Qi, L. (2020). Glucosamine Use, Inflammation, and Genetic Susceptibility, and Incidence of Type 2 Diabetes: A Prospective Study in UK Biobank. *Diabetes care*, 43(4), 719–725. https://doi.org/10.2337/dc19-1836
- 71. Vasiliadis, H. S., & Tsikopoulos, K. (2017). Glucosamine and chondroitin for the treatment of osteoarthritis. *World journal of orthopedics*, 8(1), 1–11. <a href="https://doi.org/10.5312/wjo.v8.i1.1">https://doi.org/10.5312/wjo.v8.i1.1</a>
- 72. Zhu, X., Sang, L., Wu, D., Rong, J., & Jiang, L. (2018). Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials. *Journal of orthopedic surgery and research*, *13*(1), 170. <a href="https://doi.org/10.1186/s13018-018-0871-5">https://doi.org/10.1186/s13018-018-0871-5</a>
- 73. *L-ARGININE: Overview, Uses, Side Effects, Precautions, Interactions, Dosing and Reviews.* (n.d.). WebMD. Retrieved January 24, 2022, from <a href="https://www.webmd.com/vitamins/ai/ingredientmono-875/l-arginine">https://www.webmd.com/vitamins/ai/ingredientmono-875/l-arginine</a>
- 74. Rondón, L. J., Farges, M. C., Davin, N., Sion, B., Privat, A. M., Vasson, M. P., Eschalier, A., & Courteix, C. (2018). L-Arginine supplementation prevents allodynia and hyperalgesia in painful diabetic neuropathic rats by normalizing plasma nitric oxide concentration and increasing plasma agmatine concentration. *European journal of nutrition*, *57*(7), 2353–2363. https://doi.org/10.1007/s00394-017-1508-x
- 75. Agathos, E., Tentolouris, A., Eleftheriadou, I., Katsaouni, P., Nemtzas, I., Petrou, A., Papanikolaou, C., & Tentolouris, N. (2018). Effect of α-lipoic acid on symptoms and quality of life in patients with painful diabetic neuropathy. *The Journal of international medical research*, 46(5), 1779–1790. https://doi.org/10.1177/0300060518756540
- 76. Griffin, M. (2020, November 18). *Alpha-Lipoic Acid Supplements Diabetes*. WebMD. Retrieved January 24, 2022, from <a href="https://www.webmd.com/diabetes/supplement-guide-alpha-lipoic-acid">https://www.webmd.com/diabetes/supplement-guide-alpha-lipoic-acid</a>
- 77. *What Is Benfotiamine? Benefits, Uses, and More*. (n.d.). WebMD. Retrieved January 24, 2022, from <a href="https://www.webmd.com/diabetes/benfotiamine-overview">https://www.webmd.com/diabetes/benfotiamine-overview</a>
- 78. Pavey, V., & Kiefer, D. (n.d.). *How To Block Sugar Damage With Benfotiamine*. Life Extension. Retrieved November 28, 2021, from <a href="https://www.lifeextension.com/magazine/2007/1/report\_benfotiamine">https://www.lifeextension.com/magazine/2007/1/report\_benfotiamine</a>
- 79. Sima, A. A., Calvani, M., Mehra, M., Amato, A., & Acetyl-L-Carnitine Study Group (2005). Acetyl-L-carnitine improves pain, nerve regeneration, and vibratory perception in patients with

chronic diabetic neuropathy: an analysis of two randomized placebo-controlled trials. *Diabetes care*, *28*(1), 89–94. <a href="https://doi.org/10.2337/diacare.28.1.89">https://doi.org/10.2337/diacare.28.1.89</a>