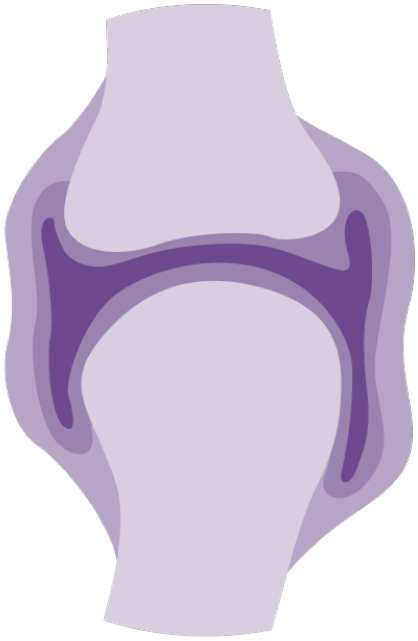
Examine®

Joint Health Supplement Guide



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Introduction

Many people with persistent and painful joint issues search for solutions, and intermittent or chronic joint pains are common in people of many ages.

Common doesn't mean simple, however. Joint health is a highly complex topic — it's not like fat loss, which, although it can be complicated in practice, nonetheless has a basic formula that underlies any successful strategy:

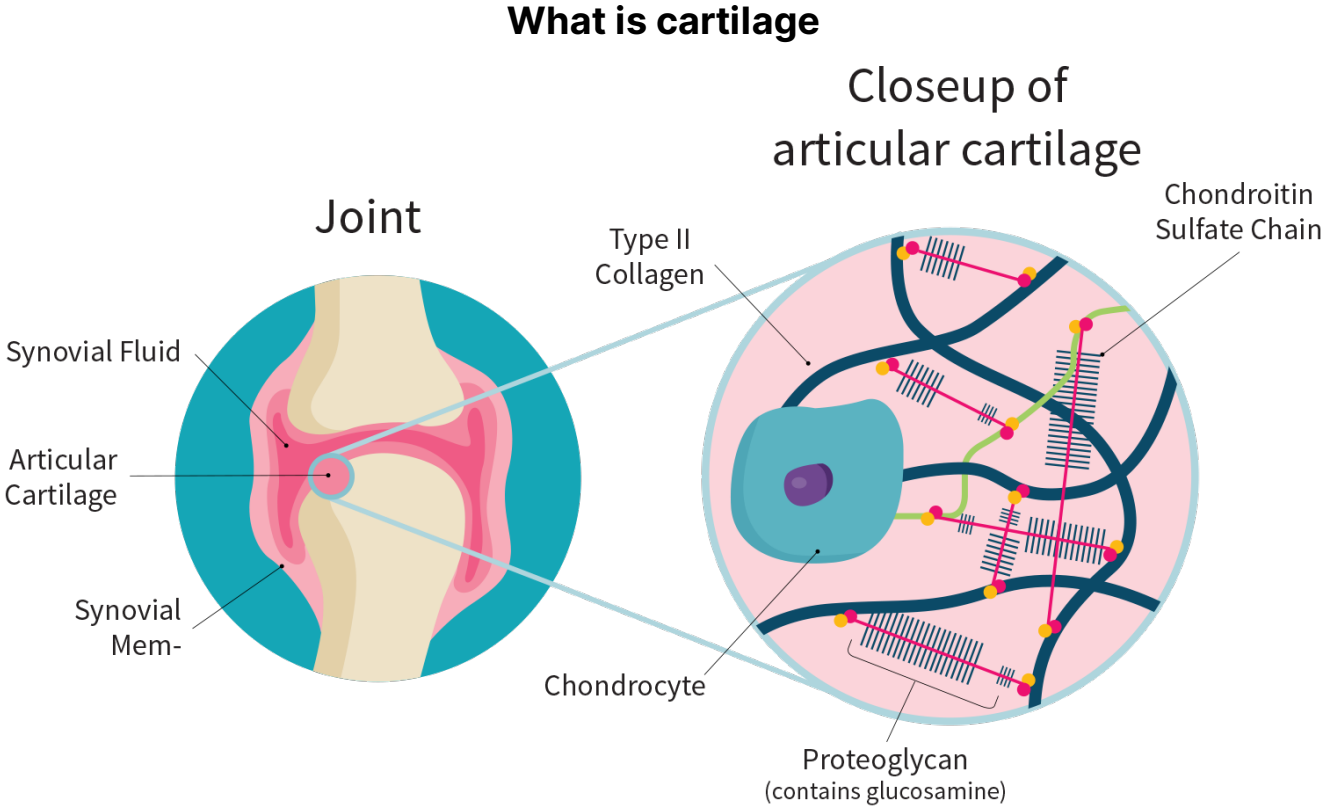
- Take in less energy than you expend.

To address joint pain, there's no formula, and the "strategy" tends to look like more this:

- Just keep trying. Don't fall for "snake oil" or useless remedies — or at least not too often.

Joint pain can affect quality of life, but it's possible to *reduce* joint pain, even if someone has "tried everything", but it definitely helps to understand a bit about joint pain physiology and why the best treatment plans aren't simple.

The reason that joint issues are so complex is quite interesting. There are many ways that joints can become damaged: by forcing past their range of motion (e.g., an ACL tear in the knee), by routinely perturbing their surroundings (e.g., by letting repetitive stress, positioning, or load compress one of the shoulder joints), or through more insidious processes (e.g., degradation due to aging, disease, or genetics). The multiplicity of possible causes, which often intersect and overlap, makes addressing joint pain difficult, as does the complexity of the joint tissue itself. The following highlights just a few components of articular cartilage:



When joints are working smoothly, people don't tend to notice or think about them at all. It's only when they stop working well — and continue to "not work" — that they become a persistent issue and a subject of persistent worry. And that's where much of the problem lies.

🔍 Digging Deeper: Weird joint pain 101

Why do some cases of joint pain resolve quickly, whereas others worsen or stay the same? Unfortunately, this topic isn't well understood,[1] and individual cases are seldom solved within a 15-minute medical appointment.

Physical therapy and anti-inflammatories (e.g., NSAIDs) may provide some relief; if neither helps, surgery may be an option. Such is the traditional approach to joint pain; it is simplistic and fraught with problems, of which we'll mention only a couple:

- Lasting joint pain can often be blamed on inflammatory tendonitis, and physicians may not look any further. It could also be caused by noninflammatory tendinosis[2] (if, for example, the tendon tissue has degenerated past the point of having an inflammatory response to injury).
- Several types of joint surgeries have recently been found to be much less effective than assumed, prompting guidelines that advise against surgery as a primary option.[3]

It's worth the trouble to ask a lot of questions. Weird joint pain is worth digging into, possibly via second opinions along with self-education. Joint pain may stem from a condition as common (yet complex and difficult to treat) as fibromyalgia,[4] or as rare as Fabry disease.[5] It could also be the result of an old injury that hasn't healed due to diet or lifestyle factors. The only way to find out is to keep exploring.

Humans, with our relatively defenseless bodies, have a fairly robust alarm system that warns our big brains that the body is indirectly in danger (for our distant ancestors, a damaged joint could easily lead to danger or death). Pain is a helpful signal when it works correctly because it helps us live out our long human lifespans. Therefore, to ensure survival, the body can become "better and better" at experiencing pain; in other words, the nervous system lowers the threshold at which signals are interpreted as painful (through varied mechanisms, notably central sensitization[6]).

Humans respond to pain much differently from most other mammals, which is why painkillers that work in animal studies often fail in human studies.[7] In humans, there is a pretty clear dichotomy: acute pain (e.g., from overexertion at the gym) responds well to medication and other interventions but chronic pain (sadly) does not.[8]

If that were the only sticking point, treatment for joint pain would be merely difficult — but joint-pain complexities don't stop there. Why did Tiger Woods rack up so many injuries after his first one? Why do individuals often develop multiple chronic conditions, with triads such as arthritic joints *plus* fibromyalgia *plus* depression? Here are three common reasons:

- *Fear of reinjury*. If you get hurt, and your performance suffers (your lifts go down or race times get worse, etc.), a bunch of things can change at once.[9] You start to compensate for the injured joint, you start to resent rehab and physical therapy, and if the pain doesn't go away, you slowly start to shy away from physical activity. In other words, you begin a cycle in which other joints get injured and you become overall less fit.

- *Sleep issues*. For people who haven't been sleeping well for months or even years, "sleep issues" is a grating euphemism. Pain can be a sleep bulldozer, with studies showing that over half of people with joint pain also suffer from disturbed sleep.[10] Sleep problems tend to worsen with the severity of joint pain, so a nagging knee injury could be merely annoying, but severe knee arthritis could stop sleep in its tracks.[11]

- *The perfect storm*. Let's say you're heading for the Olympics and aim to set up the optimal conditions to net you a gold medal. Everything you want to ensure (good sleep, support from family and friends, mental and physical well-being) is the opposite of what you'll get with chronic joint pain. Disturbed sleep is often the catalyst of this perfect storm.[12] For example, you wake up tired, your pain sensitivity is higher, your family and friends can't relate to you and sometimes get secretly annoyed, and your body feels less than ready to perform. If this cycle repeats for a few days, it's hard to climb out of the pain hole.

We've established that having chronic joint pain means turning into Sisyphus: you keep trying to roll that pain boulder up the hill, but it's too heavy. Disturbed sleep, failed treatments, fat gain and muscle loss — these factors are hard to overcome.

Luckily, thousands of studies have been conducted on joint pain. Before distilling them into tips, however, let's review three very important points.

First, remember that no single study will be the silver bullet that eliminates pain. There are so many different causes for joint pain, and only "snake oil" therapies claim to address them all. In fact, the term snake oil was originally used to describe a literal snake oil therapy for joint pain used in Traditional Chinese Medicine (TCM).

🔍 **Digging Deeper: A unified theory of pain?**

A few academics have proposed unified theories of pain, centered around areas such as inflammation or the nervous system.[13] Similarly, a plethora of researchers, academic and nonacademic, will say that there's a simple, single cause behind most of your health issues — some claim that when it comes to osteoarthritis, nightshade vegetables are the main culprit, others say that gluten is to blame for many of today's pains and ailments, and yet others state that those pains and ailments derive from a lack of direct contact with the bare earth.[14]

Common nightshade vegetables and herbs

Ashwagandha	Goji berry	Potatoes (excluding sweet potatoes)
Cayenne pepper	Paprika	Tobacco
Eggplants	Peppers/Chili peppers	Tomatoes/Tomatillos

Reference: USDA Plants Database. Accessed September 12, 2020.

It's certainly tempting to believe that a person's health issues all share a single cause because that would mean that addressing that one cause will make it all better, in one stroke. But, as implied by the very number of conflicting opinions on the nature of that cause, reality is much messier.

Admittedly, on the theoretical side, it's interesting to tie together various pain mechanisms, but the factors involved (dietary, environmental, psychological, among others) are simply too diverse to be distilled into one neat system. And yes, on the practical side, single triggers such as gluten might be at the root of multiple health issues — in *some* individuals. However, even if a person belongs to the minority of people who gluten adversely affects, embarking on a gluten-free diet isn't likely to make all of the ills magically disappear.

This is unwelcome knowledge. If chronic pain could be traced down to one cause, it would be quite easier to treat!

Second, remember that any given individual will not see immediate benefits from most therapies. Joint pain takes a while to resolve, and "a while" could range from a couple of weeks to many months. Also, different people respond differently to the same treatment because human bodies are highly variable and highly complex.

Third, remember that the benefits that any individual experiences might be difficult to assess. Pain management isn't like muscle gain or fat loss, where one can track pounds or see those biceps veins become more prominent; there is no easy way to quantify pain, and some days will be worse than others due to mysterious factors.

And now onto the "tips" (a term which greatly undersells what they are — they should instead be called Very Important Pointers That Will Help If You Follow Them).

- *Follow the sun*. No huge randomized trial has been conducted on the effect of sun exposure on pain — or on any other condition, for that matter. There's simply no financial incentive because the sun can't be patented. That said, circadian rhythm may be the most important factor in treating pain. Sunlight may decrease pain after joint surgery,[15] and UV tanning beds have been shown to decrease pain from fibromyalgia.[16] These clues are just two out of many that point to a simple message: get as much natural light as possible during the day and as little artificial bright light as you can at night.
- *Maintain a healthy weight*. This one especially matters for knee pain. During walking, each 0.5 kg (1 lb) of excess weight has the effect of about 1.8 kg (4 lb) of extra load on the knees. If a person is just 4.5 kg (10 lb) overweight, that's 18 kg (40 lb) of extra load per step — and 21,772 kg (48,000 lb) of cumulative load per 1.6 km (1 mile, assuming 1,200 steps).[17]
- *Train the brain*. It may seem that the pain is in the knee, but it's not. It's also in the brain and nervous system. Signals going up to the brain and back down to the joint modify what a person feels, so that a damaged joint that is painful to one person may hardly be felt by another.[18] Although it's not possible to "think away" joint pain, mindfulness meditation appears to reduce pain.[19] It may sound hokey, but something as minor as reframing might train the brain to perceive pain differently.
- *Help your gut bacteria help you.* No probiotic has ever been shown to universally relieve pain, probably because different people have such different microbiomes and because there's only so much one single strain can do when living among the hundreds of others in the gut. Still, certain bacterial strains have shown benefit for specific painful conditions such as rheumatoid arthritis.[20] Supplementing with probiotics matters less than general care of the gut though, like avoiding too much processed junk food.[21][22] By decreasing the chance of activating the immune system inappropriately, a happy gut microbiome leads to less pain over time.

Pain science undergoes major new developments seemingly every few months. Nevertheless, chronic pain not only persists, but more and more people have joint pain each year. Don't fall for the common trap of trying quick fix after quick fix and wasting a lot of money along the way.

A wise strategy for dealing with recalcitrant joint pain is to act slowly and mindfully: figure out which treatments are most likely to net some benefit, pick a couple, and stick with them for at least a few weeks. It's easy to try some hyped-up treatment and then be disappointed when it doesn't work. It's harder to try, over weeks and months, to soothe the brain and gut, get more sunshine, and take just a supplement or two from those presented in this guide. But joint pain is a unique enemy, and to combat it, a uniquely wise strategy is needed. Best of luck.

Kamal Patel, Co-founder and Director
MBA, MPH, PhD(c) in Nutrition

Combos

Disclaimer about supplement quality

We expect that readers will do their due diligence when choosing products. Depending on the manufacturer, supplements may have inaccurate labels (i.e., they contain too much or too little of the ingredients they claim, or in some cases, significant amounts of other ingredients not listed). They may also contain significant amounts of contaminants such as heavy metals or pesticides. It is also possible for supplements to contain ingredients that people are commonly allergic to, and it's important to be aware of the nonmedicinal ingredients as well. As a brief introduction to vetting manufacturers, we drew up a short list of steps you should take if a product has caught your interest.

> 💡 ***Tip:*** **Why don't you recommend brands or specific products?**
>
> For two reasons:
>
> - We don't test physical products. What our researchers do — all day, every day — is analyze peer-reviewed studies on supplements and nutrition.
> - We go to great lengths to protect our integrity. As you've probably noticed, we don't sell supplements or even show ads from supplement companies, even though either option would generate a lot more money than our Supplement Guides ever will — and for a lot less work, too.
>
> If we recommended any brands or specific products, our integrity would be called into question, so… we can't do it.

Core Combo

Joint pain is caused by a variety of factors. Because no supplement can address all of them, there is no core supplement in this guide.

Specialized Combos

💡 ***Tip:*** **Try one combo alone for a few weeks**

Taking too many supplements at once may prevent you from determining which ones are truly working. Start with just one of the combos suggested here for a couple of weeks before you consider making any modification, such as adding another supplement, altering the dosage of a supplement, or incorporating the supplements from an additional combo.

When adding another supplement to your regimen, be methodical. For example, you may want to take all the supplements from two combos. Select the combo that you wish to try first and take this for a couple of weeks. Next, add one supplement from the second combo and wait another week to see how it affects you. Continue this process until you've added all the supplements you want to try.

If a supplement appears in two combos that you wish to combine, don't stack the doses; instead, combine the ranges. For instance, if the range of a supplement is 2–4 mg in one combo and 3–6 mg in the other, your new range becomes 2–6 mg. Always start with the lower end of the range — especially in this case, because the reason for why one of the ranges has a lower ceiling in one combo may be due to a synergy with another supplement in the same combo. Reading through the full supplement entry may help you decide which dose to aim for, but if you're not sure, lower is usually safer.

For people with osteoarthritis

Take 400–1000 mg of Curcumin (depending on type, explained below) per day, with food, and some collagen in the form of *undenatured type-II collagen* (40 mg), *hydrolyzed collagen* (10 grams), or *gelatin* (10–15 grams).

After one month, if the results aren't satisfactory, add *Boswellia serrata* to the regimen. If that still proves insufficient, *methylsulfonylmethane* (MSM) at a total dose of approximately 3,375 mg (split into three doses of 1,125 mg each day) may improve the combo and have additional effects.

Studies on *Boswellia serrata* tend to use one of two patented extracts: *5-Loxin* and *Aflapin*. To supplement with either, take 100–250 mg once per day. Alternatively, try taking 1,800 mg of the plant's *gum oleoresin* three times a day (i.e., 5,400 mg/day).

Curcumin is a component of turmeric (aka *Curcuma longa*). Its bioavailability can be greatly increased by taking it with piperine (a black pepper extract) or by combining it with lipids (e.g., BCM-95, Meriva). To supplement *curcumin with piperine*, take 500 mg of the former with 20 mg of the latter, three times per day (i.e., 1.5 grams of curcumin and 60 mg of piperine per day). To supplement with BCM-95 or Meriva, take 500 mg twice per day (i.e., 1 g/day).

It is unclear where glucosamine and chondroitin might fit into a combo, as the main reason to take them is to reduce the rate of joint deterioration, but this is speculative. Chondroitin is generally taken in a dose of 1,200 mg of chondroitin sulfate.

For people with rheumatoid arthritis

Take 3 grams of combined EPA and DHA per day by eating fatty fish (e.g., 200 grams of salmon) or by taking

fish oil softgels (with food, to reduce the chance of fishy burps). Vegans and vegetarians have the option of taking algal oil softgels. Be sure to read the warnings section, as there is potentially a trade off with atrial fibrillation risk.

In addition, take 40 mg of undenatured type-II collagen once per day.

If there have been no improvements after a month, consider taking curcumin in the doses listed for osteoarthritis, but know that its utility for rheumatoid arthritis is still speculative, though the preliminary evidence is encouraging.

For people at risk of complex regional pain syndrome (CRPS)

Take 500 mg of vitamin C once per day, ideally in the morning.

For people with joint pain related to athletics

Try the "rheumatoid arthritis" combo above. An option is to replace the *undenatured type-II collagen* (40 mg) by some *hydrolyzed collagen* (10 grams) or some *gelatin* (10–15 grams).

Remember that **supplementation should not serve as primary treatment for injuries**. It can be used as ancillary treatment and to alleviate the pain while tending to an injury.

For people with joint pain unrelated to a disease or to athletics

Try the "rheumatoid arthritis" combo above. An option is to replace the *undenatured type-II collagen* (40 mg) by some *hydrolyzed collagen* (10 grams) or some *gelatin* (10–15 grams).

If pain persists, add the "osteoarthritis" combo above. Although collagen is a supplement in both specialized combos, taking both specialized combos doesn't mean doubling the collagen dose.

What has changed since the last time?

It should be noted that we changed the names of our ranking categories. "Core" (the highest) is now "primary", "primary" is now "secondary", and "secondary" is now "promising". This nomenclature has already been implemented for some guides, but this is the first update to the Joint Health Guide that uses this new terminology. For example, if it was a core supplement in the previous issue and now it's a secondary supplement in this issue, we'll say that it was a primary supplement in the previous issue and is now a secondary supplement.

Added:

Saffron (unproven)

Changed ranking:

Chondroitin and glucosamine

Downgraded from secondary to promising. It seems less and less likely that these supplements have clinically significant long-term effects on osteoarthritis pain and function, and there are better options for osteoarthritis. However, they may reduce long-term joint damage, though more research is needed. Pharmaceutical-grade supplements may work better, but more research is needed on that topic too.

Cissus quadrangularis

Downgraded from promising to unproven. This change is simply due to our change in evidence standards. Although it makes mechanistic sense that *Cissus quadrangularis* would help with osteoarthritis, the small number of trials that have been conducted preclude any conclusions at this time.

Clarified:

Vitamin C

Vitamin C is promising for the prevention of complex regional pain syndrome, but solid evidence supporting its use for any other source of joint pain is lacking.

Primary Supplements

Why are there no primary supplements in this guide?

Joint pain is caused by a variety of factors. Because no supplement can address all of these factors, there is no recommended primary supplement. Additionally, some supplements have a lot of supporting evidence but the effects are modest at best, or the effects look more potent but the evidence doesn't warrant a high degree of confidence.

Secondary Supplements

Boswellia Serrata

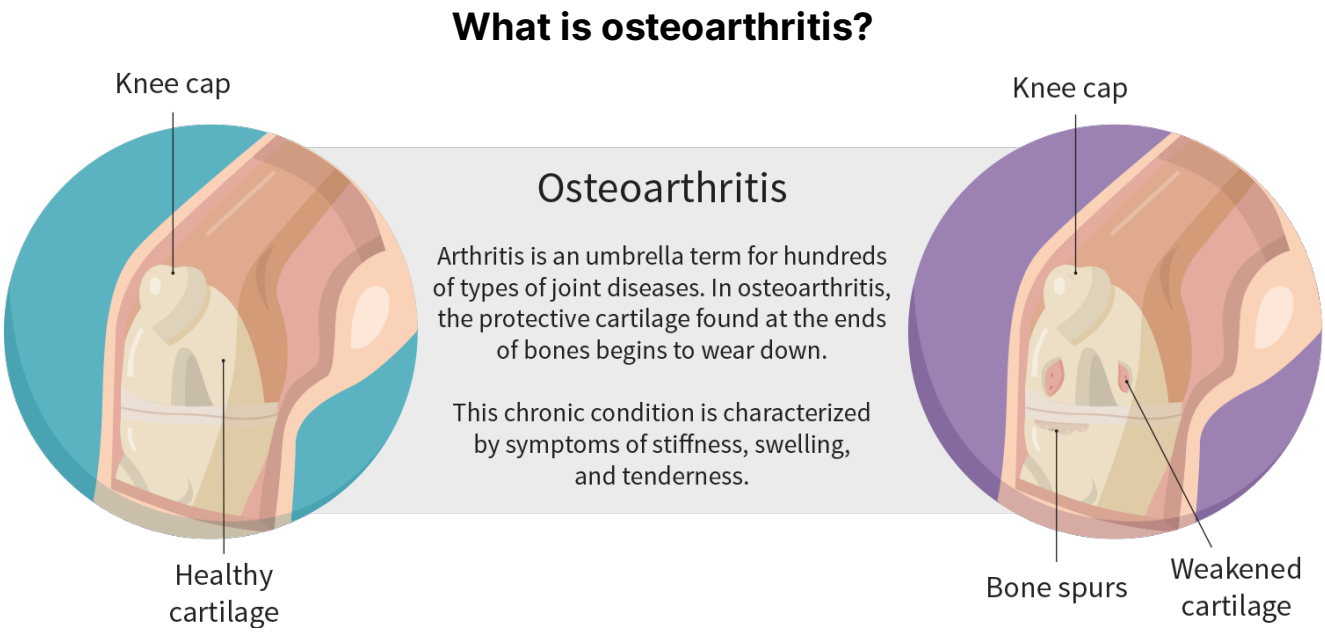
What makes Boswellia serrata a secondary supplement

Boswellia serrata is a plant used in Ayurvedic medicine primarily to alleviate joint pain. The effects of *Boswellia serrata* may largely be attributed to one of its main bioactive compounds, *acetyl-11-keto-β-boswellic acid* (AKBA), which is a potent inhibitor of 5-lipoxygenase, an enzyme responsible for inflammation.[23][24]

According to a 2020 meta-analysis of 7 randomized controlled trials, men and women with osteoarthritis who supplemented with *Boswellia serrata* or its extracts experienced small to moderate improvements in joint pain, stiffness, and function after 4 weeks of treatment.[25] Importantly, these improvements were 2–3 times greater in trials with treatment periods lasting 12 weeks. However, it's worth keeping in mind that (i) in 4 of the 7 trials, *Boswellia serrata* extract was taken together with curcumin, silverberry, or *methylsulfonylmethane* (MSM), components that may have beneficial effects on osteoarthritis symptoms of their own, and (ii) most of the trials included in the meta-analysis had an unclear or high risk of bias.

With the above said, other trials that examined the effects of *Boswellia serrata* extract on its own in participants with knee osteoarthritis have also reported large beneficial effects on osteoarthritis symptoms.[26][27][28] One of these trials examined the effects of *Boswellia serrata* extract, compared to *nonsteroidal anti-inflammatory drugs* (NSAIDs), in adults with osteoarthritis. After 6 months, the participants who took *Boswellia serrata* reported improvements in knee pain, stiffness, and function that were similar to those of the participants who took NSAIDs. Notably, one month after the cessation of the treatments, the beneficial effects were maintained only in the *Boswellia serrata* group.

More evidence is needed before *Boswellia serrata* can be said to help people with rheumatoid arthritis.



In Ayurvedic medicine, *Boswellia serrata* is often used alongside *Curcuma longa* (turmeric), a plant that contains curcumin. Further research is needed to determine whether these two supplements actually have synergistic properties.

How to take Boswellia serrata

Most studies reporting benefits of *Boswellia serrata* have used one of three patented extracts, namely, *Aflapin*, *Loxin*, and *WokVel*. *Aflapin* and *Loxin* (standardized to contain at least 20% and 30% of AKBA, respectively) have been used in daily doses of 100–250 milligrams, whereas *WokVel* (which contains around 6%–9% of AKBA) has been used in daily doses of up to 999 milligrams. Of these extracts, *Aflapin* seems to have better overall anti-inflammatory effects due to its increased bioavailability, which results in more AKBA reaching systemic circulation.[29] To supplement with *Boswellia serrata*, take 100–250 mg of Aflapin (preferably) or Loxin once per day with food. Another alternative is to take 1,800 mg of the plant's *gum oleoresin* three times a day (i.e., 5,400 mg/day).

Like curcumin, *Boswellia serrata* has been combined with lipids to increase its bioavailability (the same company that makes Meriva for curcumin makes Casperome for *Boswellia serrata*), but further research is needed to determine a dosage for joint health.

People who take *Boswellia serrata* may see a reduction in pain (e.g., −11.19 to −5.46 mm on a visual analog scale of 100 mm or −22.36 to −6.09 out of 100 on the WOMAC questionnaire pain subscale, as measured in studies). Pain may continue to improve for at least 12 weeks after beginning daily supplementation.

Warnings about Boswellia serrata

Boswellia serrata is generally well tolerated, with some reports of gastrointestinal effects including abdominal pain, diarrhea, nausea and acid reflux.[30] There are also rare reports of itchy skin and contact dermatitis (https://medlineplus.gov/ency/article/000869.htm).[31] However, studies generally haven't shown an increase in adverse events relative to control.[25][26][32][33]PMDI:28537656

There's a case study of a Boswellia extract in a skin cream causing an allergic reaction, though it's unclear how common this is.[34]

Boswellia serrata may inhibit platelet aggregation and might cause excessive bleeding, particularly in combination with blood-thinning medication.[35] However, this effect has not been evaluated clinically and is highly speculative.

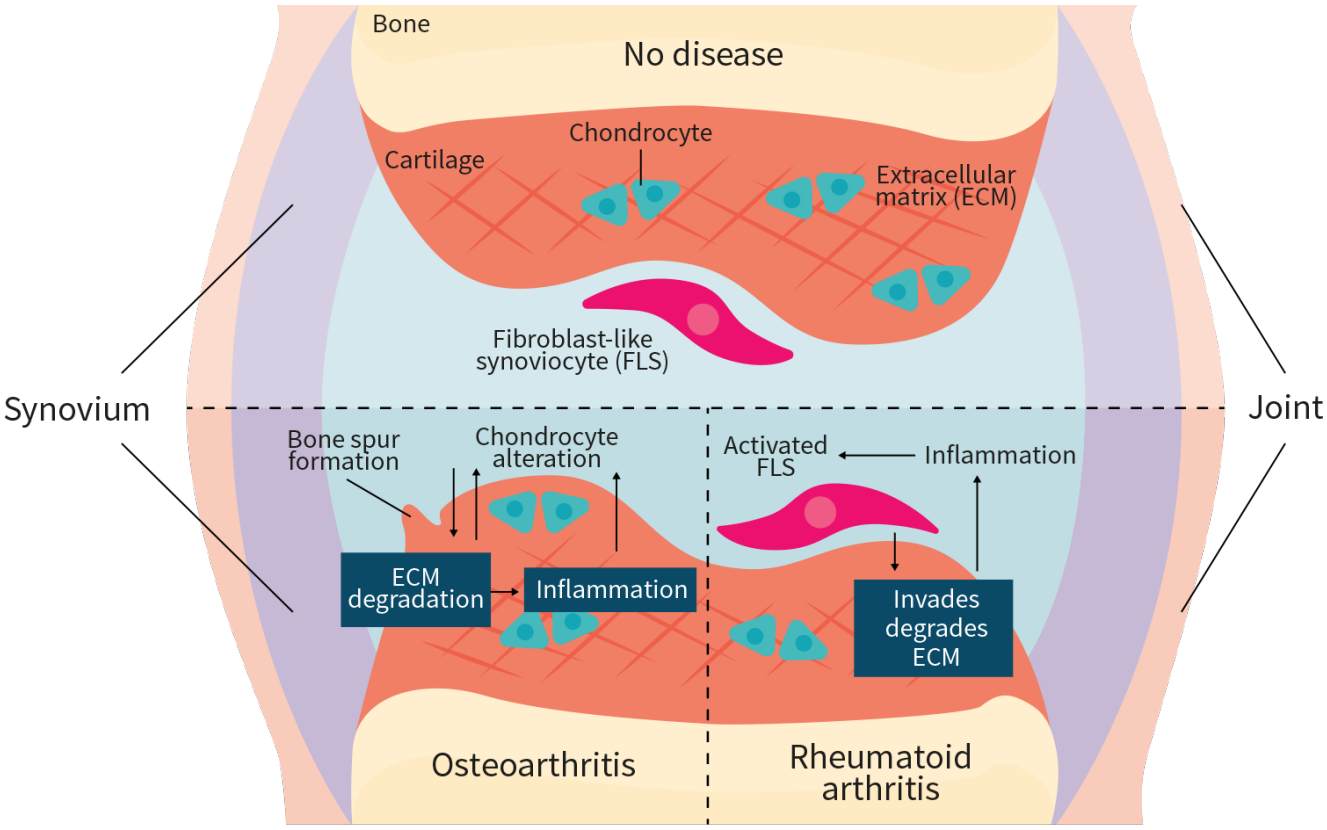
Boswellia serrata may not be safe to use in pregnancy. Although studies on this topic are inconclusive, individuals who are pregnant or planning to become pregnant should consider safer options.

[Collagen] (https://examine.com/supplements/type-ii-collagen/ #dosage-information)

What makes collagen a secondary supplement

Osteoarthritis involves damage to joint cartilage, and collagen is a major component of cartilage, so it's possible that taking collagen can help repair cartilage; this hypothesis has been demonstrated to be plausible in several preclinical studies.[36] Whole collagen won't be digested and become incorporated into cartilage directly, but it will be digested into smaller components, which can then be used to synthesize collagen.[37][38]

How cartilage degrades in osteoarthritis vs. rheumatoid arthritis



Adapted from Smolen and Aletaha. *Nat Rev Rheumatol.* 2015.[39]

The real question is always: how effective is it? Based on 13 randomized trials that evaluated collagen for osteoarthritis or other forms of joint pain, the evidence is largely in favor of modest improvements in the overall symptoms of osteoarthritis.[40][41][42][43][42][44][45][46][47][48][49][50]][51] The main reason to be skeptical of these findings, or at least of the potency of collagen, is that the available research is mainly funded by industry (or it was unclear whether it was), and although these studies used basic measures to protect against bias, there aren't enough truly high-quality trials without industry funding to have a high level of confidence in collagen.

The most effective dose of collagen isn't yet clear, but positive studies have tended to use 10 grams of hydrolyzed collagen or 40 mg of undenatured type II collagen (UCP-II).

Athletes who take collagen to prevent activity-related joint pain may see a modest benefit from 5–10 grams, but more research is needed to be precise about the optimal dose or to have confidence in its utility in this case.[52][53][54]

How to take collagen

To supplement with *undenatured type-II collagen* (UC-II), take 40 mg/day of a UC-II *cartilage* supplement, which will yield 10 mg/day of native type-II collagen.

To supplement with *hydrolyzed collagen* (also known as *collagen hydrolysate*), take 10 g/day.

To supplement with *gelatin*, take 10–15 g/day. Keep in mind that although true gelatin is composed of pure collagen (i.e., pure protein), the dessert called gelatin often has very little collagen in it.

With respect to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and expressed in terms of a 5-point scale, people taking collagen can expect a change of −0.74 to −0.08 for stiffness, but not a reliable change in pain. On a visual analog scale of 0–100 mm, however, they may see a change of −26.24 to −2.87 mm.

Warnings about collagen

Collagen appears to be safe at a dosage of up to 10 grams daily for 6 months.[45] One study found gastrointestinal side effects, including diarrhea and indigestion, but they were relatively rare, and no placebo group was used.[55] In general, studies have failed to find convincing evidence of an increase in adverse events relative to placebo. This makes sense because collagen is a protein that the body can readily digest and which is synthesized endogenously in large amounts. However, as the dose of collagen increases, the risk for gastrointestinal side effects may increase, and it's unclear what effects might occur at dosages that exceed 10 g/day. For this reason, it may be prudent to slowly increase the dose of collagen.

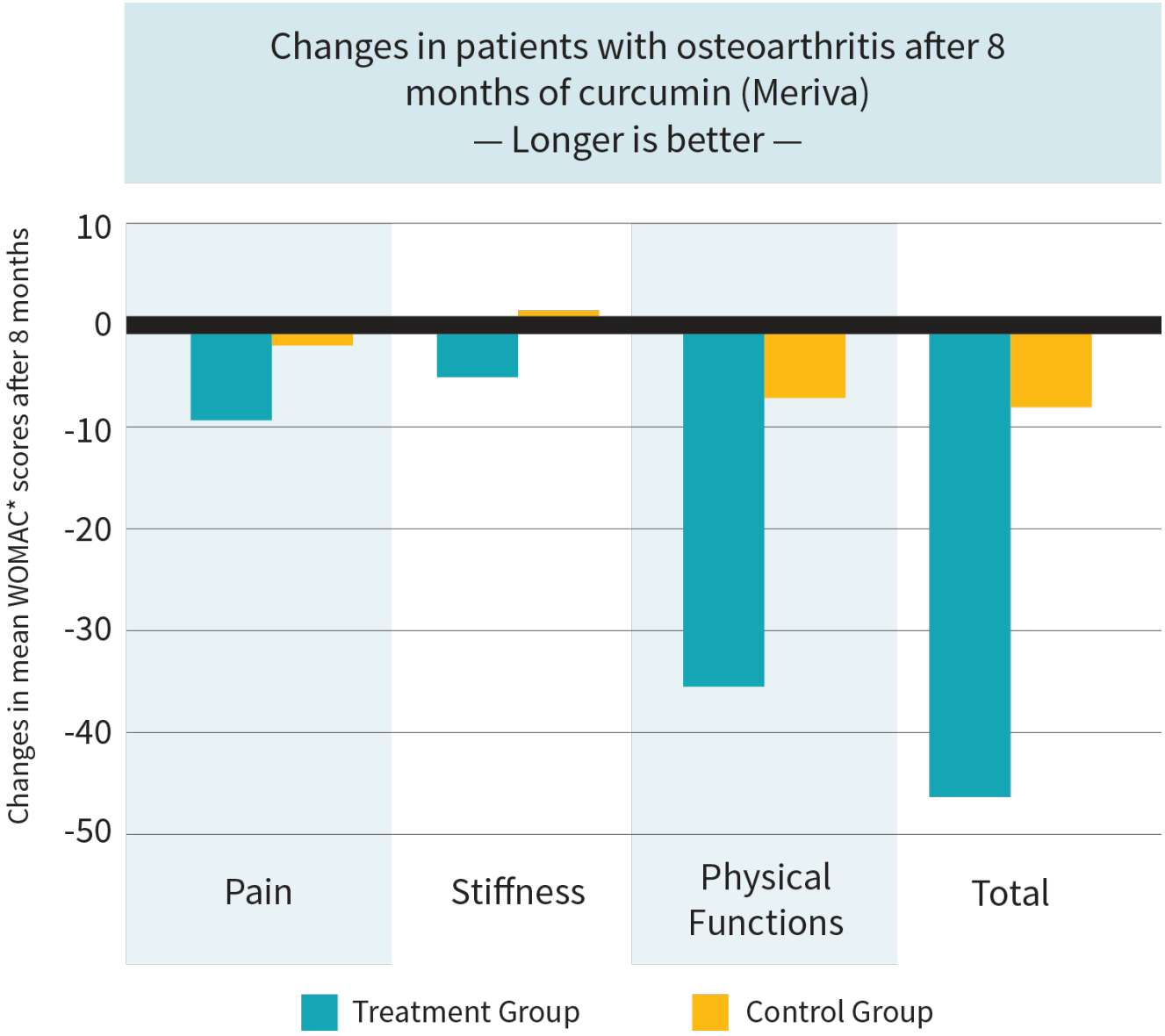
Curcumin

What makes curcumin a secondary supplement

Curcumin is a component of *Curcuma longa* or turmeric. It can inhibit *cyclooxygenase* (COX) enzymes and thus reduce inflammation in the body, so its action is similar to that of *nonsteroidal anti-inflammatory drugs* (NSAIDs).[56]

Several clinical trials have investigated the effects of turmeric extracts or curcuminoids on osteoarthritis symptoms — most commonly knee pain and physical function.[57][58][59][60][61][62][63][64][65][66][67][68][69] The results of these trials have been summarized in a number of meta-analyses.[70][71][72][73][74] Overall, the findings suggest that supplementation with turmeric extracts/curcuminoids improves osteoarthritis symptoms to a moderate–large degree, as compared to placebo, and that these effects are comparable to those of NSAIDs. One important caveat is that many of the trials were assessed as having an unclear or high risk of bias, with several trials funded by the supplement industry. Although these trials may be at a higher risk of reporting positive findings, trials of a high methodological quality and a low risk of bias have largely reported positive findings as well.

Curcumin's effects on patients with osteoarthritis



* The Western Ontario and McMaster Universities Arthritis Index is a set of questionnaires used to evaluate the condition of patients with osteoarthritis of the knee and hip.

Reference: Belcaro et al. *Altern Med Rev.* 2010.[58]

In Ayurvedic medicine, *Curcuma longa* is often used alongside *Boswellia serrata*. Further research is needed to determine whether these two supplements actually have synergistic properties.

A few trials have also examined the effects of curcumin supplementation on symptoms of rheumatoid arthritis — mainly disease activity and joint pain.[75][76][77][78]. Most of these trials have reported moderate–large improvements in disease activity and joint pain with curcumin supplementation, as compared to placebo. However, it should be noted that most of the aforementioned trials were industry funded.

How to take curcumin

By itself, curcumin is poorly absorbed. Among the methods devised to address the issue, the two most common (and most often tested) have paired curcumin with piperine (a black pepper extract) or combined it with lipids (e.g., BCM-95® and Meriva®, among others).

To supplement with curcumin + piperine, take 500 mg of curcumin with 20 mg of piperine three times per day

(i.e., 1,500 mg of curcumin and 60 mg of piperine per day).

To supplement with *BCM-95*®*, a patented combination of curcumin and essential oils, take 500 mg twice per day (i.e., 1,000 mg/day).

To supplement with *Meriva*®*, a patented combination of curcumin and soy lecithin, take 200–500 mg twice per day (i.e., 400–1,000 mg/day).

Curcumin is usually taken together with food.

People who take curcumin for osteoarthritis may see a change on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) of −1.31, which is a change of −0.24 standard deviations overall. For stiffness in particular, these changes may reach −1.29 (a change of 0.06 standard deviations), and for function, these changes may reach −2.59 (−0.27 standard deviations). On a visual analogue scale, people who supplement with curcumin may see a change in pain of −2.93 (−0.69 standard deviations).

Warnings about curcumin

Curcumin seems to be well tolerated. Some studies have reported a small amount of GI-related side effects.[79][64] Rare, individual reports of hepatitis associated with taking turmeric have also occurred.[80][81] The reason for this effect is unclear, but it is possible that it involves contamination (e.g., formulations with a high heavy metal content). It is unclear whether the same concerns apply to curcumin extract, but regardless, it is important to only buy from companies whose products have been tested independently.

Piperine is a potent inhibitor of a variety of cytochrome P450 enzymes, which is one part of what makes it a curcumin enhancer and of potential use for augmenting the effects of other drugs; in other words, it can reduce the rate of drug metabolism.[82][83][84] However, this property may make some medications more potent and lead to excessive effects. As such, it may be prudent to talk to a doctor or pharmacist before combining piperine and medications.

The same goes for curcumin itself, which has the ability to inhibit a variety of cytochrome P450 enzymes, albeit to a lesser extent.[82][85]

Curcumin may increase the risk of bleeding by interacting with anticoagulants such as warfarin (https://medlineplus.gov/druginfo/meds/a682277.html) and antiplatelets such as aspirin.[86][87] Taking curcumin with diabetes medication such as glyburide may increase the risk of low blood sugar.[88]

Some athletes use curcumin to fight muscle inflammation. In theory, curcumin should have effects similar in nature and potency to those of aspirin, and rodent studies on this aspect are promising, but human studies are needed for confirmation.

Fish Oil

What makes fish oil a secondary supplement

Fish oil is believed to be one of the most potent anti-inflammatory agents in our diet. Arthritis of the joints is an inflammatory disease, and accordingly, it seems obvious that the multifactorial anti-inflammatory effects of 20:5 (n−3) *eicosapentaenoic acid* (EPA) and 22:6 (n−3) *docosahexaenoic acid* (DHA) from fish and other

marine products like krill or algae have attracted the attention of both researchers and people with joint pain. Good evidence of the beneficial effects of fish oil exists for *rheumatoid arthritis* (RA), a condition in which a person's own immune system attacks and compromises the structural integrity of the joints.[89] Significantly less evidence exists for nonrheumatic *osteoarthritis* (OA). Although their etiologies (i.e., the specific causes and courses of the diseases) may be different, both OA and RA go hand in hand with increased levels of common markers of inflammation such as *tumor necrosis factor alpha* (TNF-α), *interleukin* (IL)-1, IL-6, IL-17, and others. Many of these cytokines are reduced in response to EPA and DHA supplements in various nonarthritic inflammatory diseases, most prominently metabolic disease.[90] Therefore, it is only mildly surprising that the results of observational and experimental studies investigating the putative beneficial effects of long-chain omega-3 supplementation in people with rheumatoid arthritis have reported positive results. In line with previous systematic reviews,[91][92][93] the results of a more recent meta-analysis of the putative benefits of fish oil supplement in people with RA[94] clearly suggest small but practically relevant reductions in disease symptoms. A systematic review by the same authors assessed 20 experimental trials (all published before the end of July 2016) that reported the use of "fish oil" from various sources. The fish oils contained between the standard 0.3 g/day of EPA+DHA found in common commercial fish oil supplements and up to 9.6 g/day of combined EPA+DHA from multiple doses of medical-grade fish oil. However, there was no evidence of existing dose-effect relationships. The study durations were between 12 and 72 weeks, and methodological differences made it difficult to weigh and compare the input data, which the researchers deemed mostly at a low-to-medium risk of bias. After pooling and analyzing the data, the authors reported a predominantly positive and small effect on the participants' subjective disease assessments (see Table 1 for an overview of selected markers), which is a positive result, albeit with effect sizes that do not warrant categorizing fish oil as a primary option. Notwithstanding the significant reductions in symptoms and although all studies were conducted in participants with RA (in whom autoimmune-induced inflammation is thought to fuel the progressive structural erosion of the joints), neither the meta-analysis nor the other currently available studies have reported consistent effects on objectively measurable blood markers of inflammation. This lack of effect on the levels of arthritis-specific blood markers and general inflammatory cytokines in the blood is a recurring theme in the literature on fish oil interventions in both people with RA and OA for whom the inflammation can be viewed as correlated with (but not the origin of) joint damage and pain. For example, one of these studies[95] recruited older and generally healthy participants with overweight and obesity. The results confirmed positive effects on arthritic pain (medium effect size) and general disease burden (small effect size), but the study authors did not observe clinically relevant improvements in markers of inflammation. Research into the influence of EPA's and DHA's direct and indirect effects on *cyclooxygenase* (COX) and *lipoxygenase* (LOX) enzymes and their competition with arachidonic acid[96] seems necessary to determine the exact mechanism behind the observable benefits for people with arthritis. Moreover, it is important to keep in mind that pain in the knees, elbows, fingers, toes, and other joints is not an age-specific or disease-specific phenomenon. Overweight and obesity are common correlates of joint pain in younger people, and transient and even chronic joint pain can also be observed in otherwise healthy, recreationally active or even athletic parts of the population with normal weights. The underlying cause of pain is often not clear, and it often predates observable osteoarthritic damage and/or rheumatoid inflammation of the sore joints. Conventional wisdom often ascribes this form of joint pain to a lack of "lubrication of the joints", which could hypothetically be restored by fish oil in the same way that WD40 lubricates mechanical junctions in cars, bikes, and other machines. Anecdotal evidence from the health and fitness community seems to confirm that hypothesis. However, scientific evidence that supports the use and usefulness of fish oil supplements in individuals without arthritic joint pain is scarce. We have found only 4 studies[97][98][99][100] that examined the effects of fish oil in participants without established arthritis and only one study in participants complaining of "mild knee pain" in the absence of diagnosed changes in joint integrity or autoimmunity.[99] That does not necessarily mean that people with mild or even no pain cannot benefit from fish oil supplements — it just leaves us with insufficient evidence to recommend fish oil as a "joint supplement" across the board. Most importantly, future studies should investigate the effects of fish oil in participants without arthritis — healthy, young, normal-weight and athletic populations, in particular. The only

study to date that at least supports the notion of preventative benefits in people without arthritis comes from the Harvard Medical School.[98] This study was a reanalysis of data from a year-long intervention study in older adults (average age of 63), without arthritis but with *coronary artery disease* (CAD), who received a relatively high dose of fish oil (1.86 grams of EPA and 1.5 grams of DHA; Lovazza™). In addition to its length and high number of participants, this study sticks out for two reasons: (a) it focused on a group with (on average) negligible joint issues at the beginning of the study, and (b) it still found improvements in joint stiffness and physical function. However, most importantly, these improvements correlated with (i) significant increases in voluntary physical activity and (ii) a reduced number of joint replacements compared to the no-treatment control group (1 vs. 11, respectively; $p = 0.002$). It should be obvious, though, that a mechanistic link between (b) improvements in joint stiffness and physical function and outcomes (i) and (ii) cannot be established. Moreover, even if the causative nature of the interaction could be confirmed, a single study in a very specific group of participants without arthritis would not warrant a general recommendation for fish oil as a proven and effective "joint supplement" with preventative effects. As a mere preventative means, fish oil must thus be rated only as a secondary option.

How to take fish oil

Take 1–3 g/day of combined EPA and DHA. Note: This number is not identical to the total quantity of "fish oil" on the label. Most commercial products contain only 180 mg of EPA and 120 mg of DHA (400 mg total of long-chain omega-3 fatty acids) per capsule. Accordingly, a person would have to take at least 3–4 capsules per day. A clear dose-response relationship has not been established. A potential superiority of EPA over DHA has been suggested but needs further investigation. The same goes for putative differences between triglyceride-bound (regular fish oil), phospholipid-bound (krill oil), and the ethyl-ester varieties doctors may prescribe.

People who take fish oil for rheumatoid arthritis may see a change in pain of −0.42 to 0 standard deviations.

Warnings about fish oil

Fish oil is known to cause gastrointestinal side effects, including abdominal pain and diarrhea, in some people.[101][102] Taking fish oil with food may help avoid these unwanted side effects.[103]

Although occurrences are rare, some cases suggest that fish oil interacts with anticoagulants like warfarin/Coumadin and antiplatelet medications like aspirin that can increase the risk of bleeding when used together.[104][105][106]. Taking fish oil alone does not appear to have this risk.[107][108] Consult with a medical caregiver or prescriber before taking fish oil with any of these medications.

There is some evidence of that fish oil increases the risk of atrial fibrillation, as detailed by Examine. The risk seems to be present even at fish oil doses as low as 1 gram. There are still many uncertainties (including the magnitude of risk) as to whether or not this risk is present in people without cardiovascular disease or who are not at a high risk of cardiovascular disease.

🔍 *Digging Deeper:* Oxidized fish oil

Fish oil can become rancid and oxidize when exposed to oxygen, heat, or light. These types of oil are particularly susceptible to oxidation because of their very-long-chain polyunsaturated fatty acids. The oxidation level is measured using three values:

1. *Peroxide value* (PV)
2. *Anisidine value* (AV)
3. *Total oxidation value* (TOTOX)

PV is a measure of primary oxidation products (peroxides), and AV is a measure of secondary oxidation (aldehydes and ketones). The TOTOX value is calculated using the formula AV + 2PV. The lower the TOTOX value, the better the oil quality will be. The Global Organization for EPA and DHA Omega-3 recommends a TOTOX value of no more than 26.

Oxidation of fish oils may be more common than many suspect. One 2015 study found that nearly 50% of commercial fish oils exceeded the maximum recommended TOTOX value,[109] whereas others found good compliance with TOTOX limits.[110][111] Taken together, these divergent results demonstrate just how widely the quality of commercially available fish oil supplements can vary.

Evidence for the health effects of consuming oxidized fish oils is a bit mixed. For healthy individuals, there is a lack of obvious short-term health damage from consuming oxidized fish oil. One study showed no difference in circulating levels of oxidized LDL or inflammatory markers after 7 weeks of supplementation with oxidized fish oil.[112]

However, in participants with high levels of cholesterol and triglycerides, consumption of highly oxidized fish oils can minimize its efficiency in improving metabolic markers such as fasting glucose, total cholesterol, and triglycerides.[113]

Promising Supplements

Chondroitin and Glucosamine

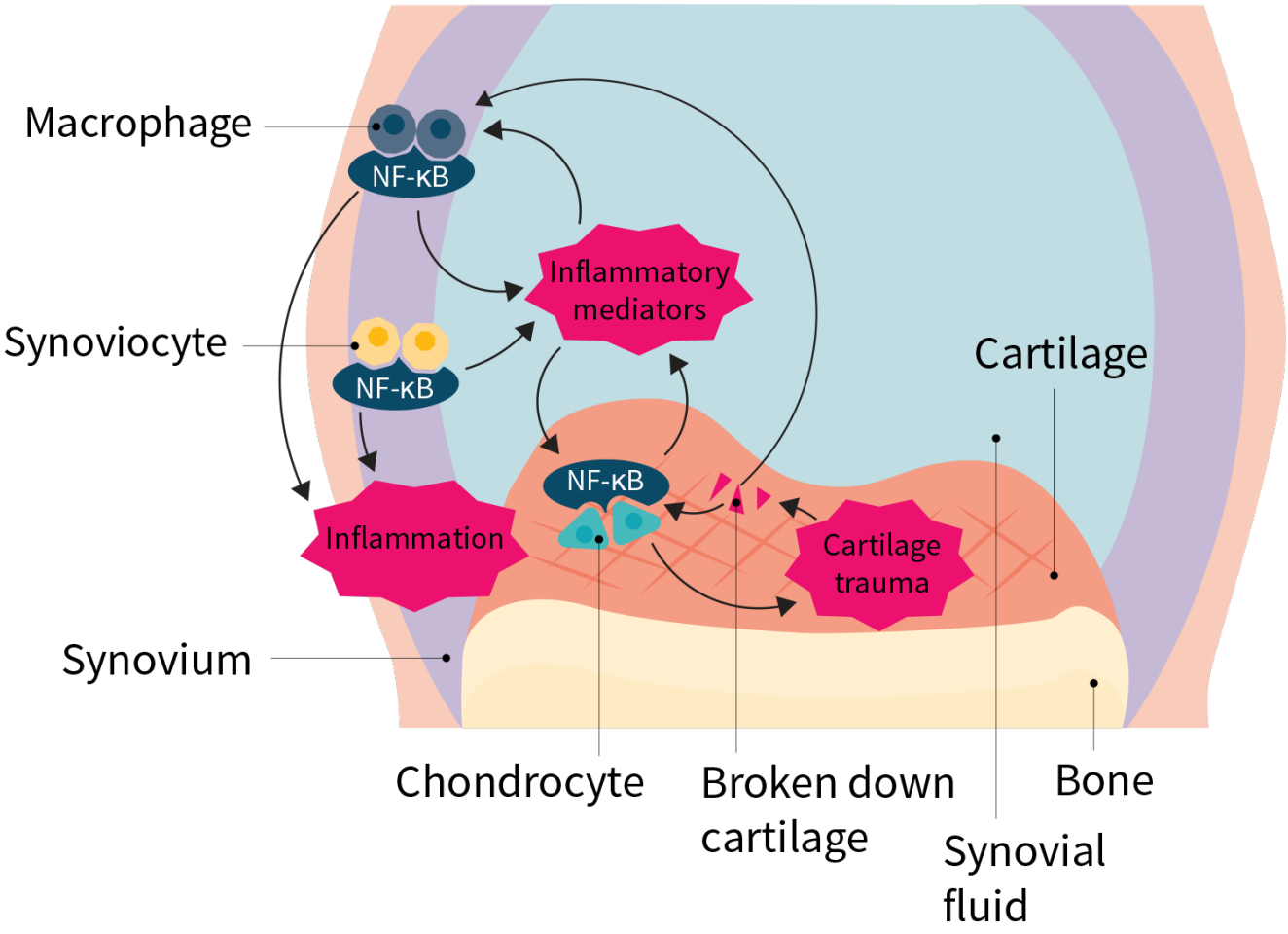
Why has there been so much interest in chondroitin and glucosamine?

Chondroitin and glucosamine are basic components of cartilage and synovial fluid and are popular supplements for osteoarthritis due to the possibility that they could help to repair cartilage and balance the ratio between catabolism and anabolism in osteoarthritic cartilage.[114][115]

In addition to a direct structural role, these components also have anti-inflammatory effects, which could reduce the progression of osteoarthritis and relieve symptoms.

Chondroitin's anti-inflammatory effects might occur through inhibition of the protein complex NF-κB, which regulates inflammatory responses.[116]

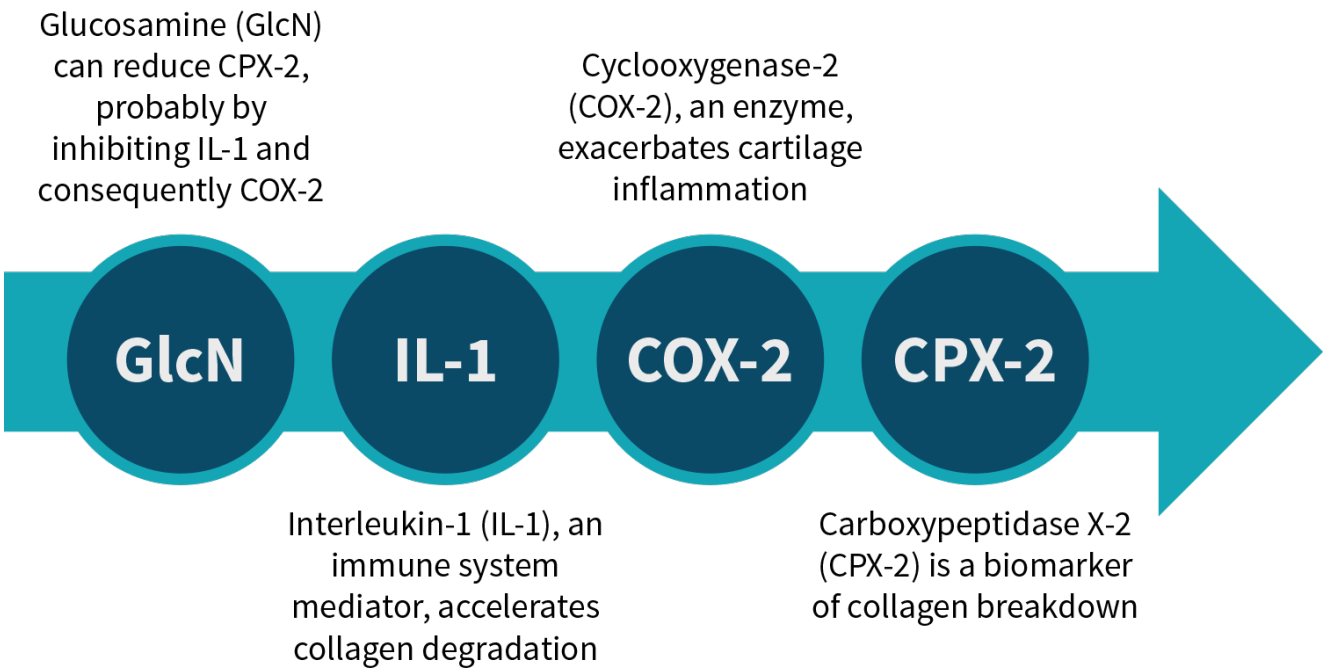
Putative inflammatory interplay between the synovium and cartilage



Adapted from Lovu et al. *Osteoarthritis Cartilage*. 2008.[116]

Glucosamine may reduce COX-2 activity and the subsequent inflammatory response.[117]

Glucosamine's cartilage-preserving effects



What makes chondroitin a promising supplement

A meta-analysis of randomized double-blind trials that tested the effects of chondroitin sulfate on osteoarthritis pain and structural changes found a small but statistically significant reduction in pain.[118] This reduction wasn't affected by limiting the analysis to studies without industry involvement (industry involvement has been a frequent concern with chondroitin research). The effect was smaller but still statistically significant when only considering studies with high methodological quality. A small but statistically significant reduction in joint-space narrowing was found overall but was considerably diminished when factoring in industry involvement and was no longer statistically significant when considering only high-quality studies. However, these two subgroup analyses involved far fewer studies than for pain.

Another meta-analysis of 18 randomized controlled trials found a moderate and statistically significant reduction in pain and a small improvement in physical function.[119] These effects on pain and physical function were lower in the longest studies. Studies at a low risk of bias also had considerably smaller effect sizes than studies with a high risk of bias, though the effect was still statistically significant when considering only low-risk studies.

Another meta-analysis that considered only randomized trials that lasted 6 months or longer didn't find a meaningful effect on pain or function overall, although it found a small, statistically significant effect for pharmaceutical-grade chondroitin.[120] Another meta-analysis of randomized trials lasting 12 months or longer found a small but statistically significant effect on joint space/cartilage volume but no clear evidence for a benefit to pain or function.[121]

In summary, chondroitin is unlikely to have a meaningful effect on pain and physical function in the long term. However, it might reduce the rate of cartilage degradation, though research is still insufficient on that topic, and more high-quality studies are needed.

Warnings about chondroitin

Oral supplementation with chondroitin is relatively safe, and it hasn't been known to increase overall adverse events relative to placebo in trials on osteoarthritis.[122] Some adverse events including musculoskeletal problems, connective tissue problems, skin problems, headaches, and a variety of gastrointestinal symptoms have been reported.[123][124][125] However, it isn't clear that these adverse events are particularly caused by chondroitin.

Chondroitin and glucosamine may have anticoagulant properties, which could be a problem for people taking blood thinners, such as antiplatelet agents (e.g., aspirin) or anticoagulants (e.g., warfarin/Coumadin and acenocoumarol/Sintrom).[126][127]

It is possible that people with shellfish allergies could experience reactions from chondroitin, though this may be due to combinations that include glucosamine, which is often produced from the shells of shellfish.[128]

How to take chondroitin

Take 600–1,200 mg of *chondroitin sulfate* per day, with food. Within this range, higher doses may be more effective.

Talk to a physician to find out whether pharmaceutical-grade chondroitin is a viable treatment option for a particular circumstance because this type of chondroitin may be more effective.

In the short-term (less than 3 months), people taking chondroitin may see a change in pain of −0.59 to −0.22 standard deviations. It is unclear whether chondroitin can offer consistent long-term reductions in pain.

There may be a reduction in joint space narrowing of −0.61 to 0.00 standard deviations over the course of 12 months.

What makes glucosamine a promising option

A meta-analysis of 17 randomized double-blind trials on glucosamine sulfate found a small but statistically significant reduction in pain.[129] When the 6 studies with industry involvement were excluded, the effect was even smaller — not what would be considered clinically significant on its own, but if genuine, it could be a potentially good addition to a supplement combination; the same held true for comparison of studies with low and high methodological quality and in the case of joint space as well.

Another meta-analysis restricted the included studies to those lasting 6 months or longer and found a general lack of effect on pain and physical function, although it did find a small, statistically significant effect for prescription crystalline glucosamine, based on a small number of studies.[120] Yet another meta-analysis included studies that assessed joint space width or cartilage volume over the course of 12 months or longer and found a small and not statistically significant effect.[121]

The effect of glucosamine on pain is small, and the methodological shortcomings of some of the studies limit confidence in the small effect. The effect isn't large enough to warrant confidence that glucosamine will have a meaningful effect on pain in the long-term, though there is a possibility that it could reduce the degradation of joints. However, this possibility is also questionable but can't be ruled out.

Warnings about Glucosamine

Oral supplementation with glucosamine is relatively safe, and it hasn't been known to increase overall adverse events relative to placebo in trials on osteoarthritis, except for a possible increase in musculoskeletal adverse events (though this is based on insufficient evidence to be confident in it[122]). Individual studies have found a somewhat higher rate of respiratory tract adverse events, arthralgia, and gastrointestinal adverse events.[130][131][132][55] However, these observations haven't been corroborated by other studies and could easily be due to chance.

Some studies suggest that glucosamine sulfate supplements may have a negative effect on glucose metabolism. This effect may confirm observations from *in vitro* and rodent studies that revealed that glucosamine inhibits beta-cell glucokinase activity and thus induces a metabolic state similar to *non-insulin-dependent diabetes mellitus* (NIDDM).[133] More recently, glucosamine has mostly been cleared of being a prodiabetic agent in most practical cases, with the putative exception of individuals with untreated diabetes or glucose intolerance.[134] Systematic reviews, on the other hand, show no general ill effect of glucosamine supplements on glycemia in healthy individuals and highlight that there is insufficient evidence of prodiabetic effects in individuals with type 2 diabetes or prediabetes.[135][136]

Glucosamine and chondroitin may have anticoagulant properties, which could be a problem for people taking blood thinners such as antiplatelet agents (e.g., aspirin) or anticoagulants (e.g., warfarin/Coumadin and acenocoumarol/Sintrom).[126][127]

It is possible that people with shellfish allergies could experience reactions from glucosamine because it is commonly produced from the shells of shellfish.[128]

How to take glucosamine

Take 1.5 grams of *crystalline glucosamine sulfate* (a stabilized form of glucosamine sulfate).

Glucosamine sulfate sodium chloride is the best-studied form of crystalline glucosamine sulfate, but preliminary evidence suggests that *glucosamine sulfate potassium chloride* may be equally efficacious.

Studies do not support the use of other types of glucosamine sulfate. Studies do not support the use of glucosamine hydrochloride.

People who take glucosamine may see a change in pain of −0.54 to −0.16 standard deviations. It is unclear whether glucosamine can offer consistent long-term reductions in pain.

Glucosamine may lead to a change in joint-space narrowing of −0.23 to +0.04 standard deviations over the course of 4–5 months.

Glucosamine + Chondroitin

A meta-analysis of randomized controlled trials on the combination of glucosamine and chondroitin found a lack of effect on pain, physical function, or stiffness when the combination was compared to a placebo, based on a small number of studies.[122] Another meta-analysis on randomized trials lasting 6 months or longer failed to find a meaningful effect of glucosamine + chondroitin on pain, function, or joint space narrowing, also based on a small number of studies.[120] The reason for why the combination is said to be ineffective here — compared to reports of efficacy in the previous sections — is that the individual supplements have a small

short-term effect, likely due to the different characteristics of the different studies.

Warnings about Glucosamine + Chondroitin

Individual warnings about glucosamine or chondroitin from the previous sections apply to their combination. Additionally, when used in trials, the combination of glucosamine and chondroitin appears to carry a greater risk for gastrointestinal, central nervous system, musculoskeletal, infection-related, and other adverse events. However, this caution is based on too little research to comfortably rule out random chance, and we aren't very confident in the findings. It would make sense that taking both could amplify the risk of adverse events though, so caution should be taken. Using lower doses for each component than one would take individually could be prudent.

MSM

What makes *MSM* a promising option

Methylsulfonylmethane (MSM) is an organosulfur compound that has the potential to control chronic inflammation, which makes it a plausible candidate for osteoarthritis treatment.[137][138] Furthermore, it seems to have glutathione-maintaining properties and can reduce lipid and protein oxidation, which may give it additional protective effects.[139]

Four randomized double-blind studies on osteoarthritis have been conducted, each lasting 12 weeks; the results showed general improvements in pain, physical function, and overall symptom scores when measured.[132][140][141][142] Although this evidence is promising, the main reservation with MSM is the lack of research compared with other supplements. The size and consistency of effects for the average person with osteoarthritis are still unclear, and it's also unclear whether MSM has any unique effects that would warrant inclusion in a supplement stack.

The effects on pain related to exercise are unclear and the small amount of research available so far is negative.[143][144]

Warnings About *MSM*

MSM appears to be highly safe, and the studies that evaluated adverse events failed to find a meaningful safety difference between it and placebo. One study found a slightly higher incidence of bloating and insomnia compared with placebo; however, this finding is unreliable and could easily be due to chance.[140] In one study, a basic blood test failed to find differences for various safety biomarkers compared with placebo.[145]

More studies on the long-term use of MSM are needed to declare it to be truly safe, but there appears to be little risk in the short-term.

How to take *MSM*

The study with the greatest effect used 1,125 mg three times a day (i.e., 3,375 mg/day). There is no proven

benefit to taking more than 6 grams per day, and the optimal and sufficient doses are generally unclear.

MSM has been tested with *Boswellia serrata*, with glucosamine, and with a combination of glucosamine and chondroitin. In each case, the addition of MSM seems to confer a slight benefit, but further research is needed for confirmation.

An estimation of MSM's effect size isn't possible at this time.

Pycnogenol

What makes *Pycnogenol* a promising option

Procyanidins are flavonoids that may improve blood flow and reduce inflammation. Pycnogenol is a patented extract made from the bark of the French maritime pine (*Pinus pinaster* Aiton) that is standardized to contain 65%–75% procyanidins. To date, 3 trials investigating the role of Pycnogenol in the management of osteoarthritis have been published.[146]DOI:10.1016/j.nutres.2007.09.007[147] All trials were double blinded, randomized, and placebo controlled and looked at the effects of supplementation with 100 or 150 milligrams of Pycnogenol for three months on osteoarthritic symptoms (knee pain, knee stiffness, and physical function) in men and women with mild osteoarthritis (Grade 1 or 2).

Overall, the aforementioned trials reported positive effects of Pycnogenol supplementation on knee pain, knee stiffness, and physical function, with moderate to large effect size. That said, the available trials are few and are of unclear or high risk of bias. Moreover, at least 2 of the trials were funded by the manufacturers and patent owners of Pycnogenol. As such, although promising, the available evidence should be considered preliminary.

Grape seed extract is rich in procyanidins and lower in cost than pine bark extracts, but its benefits on joint health have never been directly demonstrated.

Warnings about *Pycnogenol*

Reported side effects from pycnogenol use are rare but include gastrointestinal discomfort, nausea, headache, and dizziness.[148] Taking pycnogenol with food could decrease your chances of having adverse GI effects.[149]

Taking a pine bark extract with other hypotensive agents could cause low blood pressure. Hypotensive agents can be pharmaceuticals as well as supplements (notably garlic) but also nitrates, cocoa, or grape seed extracts, to mention only the supplements presented in this guide.

How to take *Pycnogenol*

To supplement with *Pycnogenol*, take 50 milligrams 2–3 times per day with meals, for a total daily dose of 100–150 milligrams.

The maximum benefit is usually experienced after 2–3 months of continuous supplementation.

Judging from a study on a grape seed extract, the improvement in blood flow from pine bark extracts might

be negated by the flavonoid quercetin, so concurrent supplementation should therefore be avoided.

An estimation of pycnogenol's effect size isn't possible at this time.

Saffron

The term "saffron" refers to both the perennial stemless herb *Crocus sativus* that is primarily cultivated in Iran, Spain, India, and Greece and to the deeply orange aromatic spice that is derived from the dried stigmas in the blue-purple flowers of the crocus plant. This fine powder is best known for its unique flavor and is one of the most expensive culinary spices on the market. Saffron contains more than 150 different antioxidant compounds, which are also thought to contribute to its supposed medicinal benefits.[150]

What makes *saffron* a promising option

Both regular saffron powders and crude aqueous/ethanolic extracts, as well as specific extracts containing primarily one or a specific mixture of saffron's purportedly pharmacologically active carotenoids (i.e. crocetin, crocin, or safranal), have been found to reduce oxidative stress and inflammation *in vitro* and *in vivo*. Many of the pertinent studies were conducted in rodent models. The corresponding studies reported preventative effects on ulcers, general improvements in digestion, and benefits in cancer treatment and prevention, heart and metabolic health, and glucose metabolism, as well as antidepressant, anxiolytic, and hypnotic effects.[151] In addition, there is some evidence to suggest that the anti-inflammatory effects of saffron extracts, and particularly those of crocin, can ameliorate arthritic pain [150]. Currently, there are only 2 human studies to support a pain-reducing effect in arthritis. A 12-week double-blind randomized controlled trial conducted at the Iran University of Medical Sciences found significant improvements[152] using the validated arthritis-specific *28-item disease activity score* (DAS28).[153][154] The DAS28 ratings range from ≤ 2.5 (indicating remission) to ≤3.2, ≤ 5.1, and >5.1 for low, medium, and high disease activity, respectively. The ratings are based on objectively measurable signs of inflammation such as swelling or redness, as well as markers of self-reported pain intensity. In the first study, significant reductions in DAS28 score (−0.75) from high-medium to low-medium disease activity and significantly lower CRP values were observed in response to 100 mg of saffron powder per day taken by 61 women (average age of 53) with *rheumatoid arthritis* (RA).[155]. In the second study, [156] which was also conducted by Iranian researchers, 40 participants (ages 40–70) with medically diagnosed osteoarthritis (67% women, 33% men), the participants received one capsule per day for 4 months of a commercial Iranian saffron extract (Krocina™; the authors declared "no conflict of interest") standardized for 15 mg of crocin with generally similar self-reported outcomes that were quantified on a simple visual analogue scale from 0 to 10 (preintervention: 7.83, postintervention: 2.27), and improvements were also observed in the placebo group (preintervention: 8, postintervention: 6.7). Thus the efficacy of the supplement remains questionable.

Warnings about saffron

A meta-analysis of randomized controlled trials on saffron and depression found a potential modest increase in headaches, anxiety, tremors, heart palpitations, sweating, nausea, vomiting, increased appetite, and other gastrointestinal complaints; however, none of these increases reached statistical significance, and the average expected incidence remains unclear.[157] Another meta-analysis reported a lack of severe adverse events.[158] In one study, 26 weeks of supplementation with 60 mg of saffron extract in men was associated with reductions in red and white blood cell counts and in platelets, along with a drop in systolic and diastolic blood pressure of 10.8%–11.7% and complaints of sedation, hypomania, and changes in appetite, which started to occur after

8 weeks of exposure and increased in magnitude as the study continued.[159] One review paper suggested that the side effects of dosages below 1.5 g/day are rare, though there are some reports of 1.2 to 2 grams possibly causing vomiting, diarrhea, and bleeding. [150]. In their review, Schmidt et al. reported potentially abortive effects of >10 grams of saffron powder in pregnant women, though this report dates back to 1925 and could be the result of the presence of unwanted pollutants in the formulation. Saffron likely reduces blood sugar, and in combination with diabetes medication, it could possibly lead to hypoglycemia. Saffron may also reduce blood pressure, and in combination with hypertension medication, it could possibly lead to low blood pressure. Natural chemicals in saffron can interfere with the activity of cytochrome P450 enzymes, which could either reduce or increase the rate of metabolism for various drugs, potentially leading to negative interactions.[160]

How to take saffron

Daily dosages of 100 mg/day of regular saffron and extracts containing 10–20 mg/day of active ingredients have been found to be efficient (regardless of timing), not only for arthritic pain and inflammation but also as natural antidepressants, with a potency similar to that of well-established antidepressant drugs [161][162]. An estimation of saffron's effect size isn't possible at this time.

Vitamin C

What makes *vitamin C* a secondary option

Vitamin C is necessary for collagen formation, so having low levels of vitamin C can be detrimental to joint health. However, in people whose levels are normal, supplemental vitamin C has little effect on joint disorders, with one exception: it can help prevent *complex regional pain syndrome*(https://medlineplus.gov/complexregionalpainsyndrome.html) (CRPS), a painful chronic condition characterized by swollen joints and by changes in skin quality and hair quality. CRPS can be caused by orthopedic surgery or a joint injury.

Warnings about Vitamin C

Vitamin C can potentially cause diarrhea, nausea, and stomach cramps. Taking vitamin C can cause dental erosion.[163] Logically, the risk is probably more likely with powders taken in liquid or chewable tablets, and a fully encapsulated vitamin C supplement would likely not have this effect. Supplemental doses of vitamin C may reduce some of the cellular adaptations to exercise, namely, mitochondrial biogenesis and endogenous antioxidant synthesis.[164][165] It is unclear how long this effect persists after dosing, so it may be best to leave as much time as possible between vitamin C supplementation and exercise. Vitamin C likely reduces blood sugar, and in combination with diabetes medication, it could possibly lead to hypoglycemia. Very high doses of vitamin C may sometimes damage the kidneys by being metabolized into oxalate,[166] and this may lead to renal failure in rare cases.[167][168][169] The lowest dose needed to see a concerning rise in urinary oxalate is 1 g/day. Vitamin C may also reduce blood pressure, and in combination with hypertension medication (https://medlineplus.gov/bloodpressuremedicines.html), it could possibly lead to low blood pressure Vitamin C may reduce the effectiveness of some HIV medications. Moreover, because it can increase the absorption of iron and aluminum, it should not be taken within several hours of taking aluminum-based antacids (e.g., Amphojel, AlternaGEL, Alu-Cap, Alu-Tab, Dialume).

How to take *vitamin C*

People at risk of CRPS can take 500 mg of vitamin C once per day, ideally in the morning.

People with joint pain not associated with CRPS can also take 500 mg of vitamin C once per day, but if the pain has not lessened after 2 months, supplementation need not be continued.

Further research is needed to determine whether vitamin C is better absorbed with food.

The Recommended Dietary Allowance (RDA) of vitamin C for adults ranges from 75 to 120 mg per day.[170] Although the 500 mg/day dosage discussed here exceeds the RDA, it is still well under vitamin C's Tolerable Upper Intake Level (UL) of 2,000 mg/day.

Tolerable Upper Intake Level (UL) for vitamin C (mg)

AGE	MALE	FEMALE	PREGNANT	LACTATING
0–12 months	*	*	—	—
1–3 years	400	400	—	—
4–8 years	650	650	—	—
9–13 years	1,200	1,200	—	—
14–18 years	1,800	1,800	1,800	1,800
>18 years	2,000	2,000	2,000	2,000

* Formula and food should be the only sources of vitamin C for infants.

Reference: Institute of Medicine. Vitamin C (chapter 5 in *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. The National Academies Press. 2000. DOI:10.17226/9810)

Unproven Supplements

CBD (cannabidiol)

What makes *CBD* unproven

CBD (cannabidiol) is the second most abundant cannabinoid in cannabis (aka marijuana, after THC (tetrahydrocannabinol).[171] Isolated CBD is typically used medicinally, not recreationally, and the four most commonly targeted conditions are pain, anxiety, depression, and sleep disorders.[172]

The Arthritis Foundation is an advocacy group based in the United States. One of their aims is to provide evidence-based resources for people with arthritis. A recent survey that they conducted found that 30% of the respondents used CBD, and close to 80% were considering using it or have used it previously.

The large and growing interest in CBD prompted The Arthritis Foundation to release a set of expert-reviewed guidelines for people with arthritis who are interested in using CBD. The key takeaways are summarized below. Another review by the National Academies of Sciences, Engineering, and Medicine also found that studies on CBD and arthritis were very limited at the moment.[173]

Cissus quadrangularis

As used in traditional medicine in both Asia and parts of Africa for centuries, the stems and leaves of *Cissus quadrangularis* L. (aka Cissus) have more recently attracted scientists' attention as an anti-inflammatory medicinal compound. Its historically well-documented effects are ascribed to Cissus' relatively high content of antioxidants like vitamin C and beta-carotene and various ketosteroids, flavonoids, and phytosterols.

What makes *Cissus quadrangularis* an unproven option

There is no good evidence to support the claims about Cissus' effects on joint health. In fact, there is only one publication that appropriately reported both methods and outcomes of a pilot study that was specifically designed to test its antiarthritic effects [174]. The study was at best of exploratory nature, had no placebo control (not even a “no treatment” control), recruited only 29 participants, and had no preregistration of the experimental protocol, no objectively measurable primary outcomes, no *a priori* (or *ex post*) power calculation, as well as a dubious potential influence of "partial" industry funding. All these shortcomings undermine confidence in the allegedly “promising” results that were reported, namely, a significant improvement in the McMaster Universities Osteoarthritis Index (WOMAC) index, [175] a common, repeatedly validated composite index of symptoms and physical function in people with OA of the knee and the hip, and the subjective workout-related pain ratings that the researchers collected before and after an 8-week intervention using 3 grams per day of *Cissus quadrangularis* given in capsule form. The other paper that specifically addressed the use of Cissus for joint health was also a non-(placebo-)controlled,

nonpreregistered study.[176] In the study, the authors recruited 60 Indian participants (31–70 years) with obesity and a diagnosis of osteoporosis or bone spurs (osteophytic changes). The participants were assigned to one of three treatments: 5 grams twice daily of *Cissus quadrangularis*, 5 grams twice daily of *Zingiber officinale* (commonly known as "ginger"), or a combination treatment with both. The total study duration was not properly reported, but with questionnaires handed out at three 15-day intervals, it seems logical to assume that it took 45 days for the subjective improvements in joint swelling (from “moderate” to “normal”) and tenderness (from “mild” to “normal”) to manifest. Due to the use of an unvalidated questionnaire and a rather dubious pain scale ranging from 0 = normal to 3 = severe, the results must be taken with caution. In the absence of control and/or placebo groups in both of the relevant studies, it is clear that *Cissus quadrangularis* must be considered as "unproven" with respect to its putatively beneficial effects on joint health.

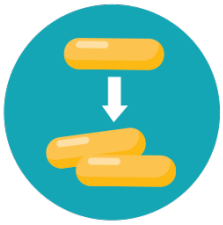
Key takeaways from The Arthritis Foundation’s CBD guidelines

While CBD may be effective for pain, anxiety, and insomnia related to arthritis, its efficacy isn’t backed by strong clinical trials yet.

CBD may interact with steroidal and non-steroidal anti-inflammatory drugs, some antidepressants, tofacitinib and some fibromyalgia meds like gabapentin.

Don’t replace disease-modifying drugs with CBD!

Before starting CBD, discuss it with your doctor and follow up approximately every three months if you do start it.



There’s no clear dosing schedule yet, but doses should generally start low and slowly titrate up over several weeks if the lower dose doesn’t work. If it doesn’t work after several weeks or if side effects kick in, CBD may not be a good choice.

Only buy CBD from reputable companies that use independent labs that test for purity and potency, and can provide a certificate of analysis.

Reference: Arthritis.org

Inadvisable Supplements

Thunder God Vine

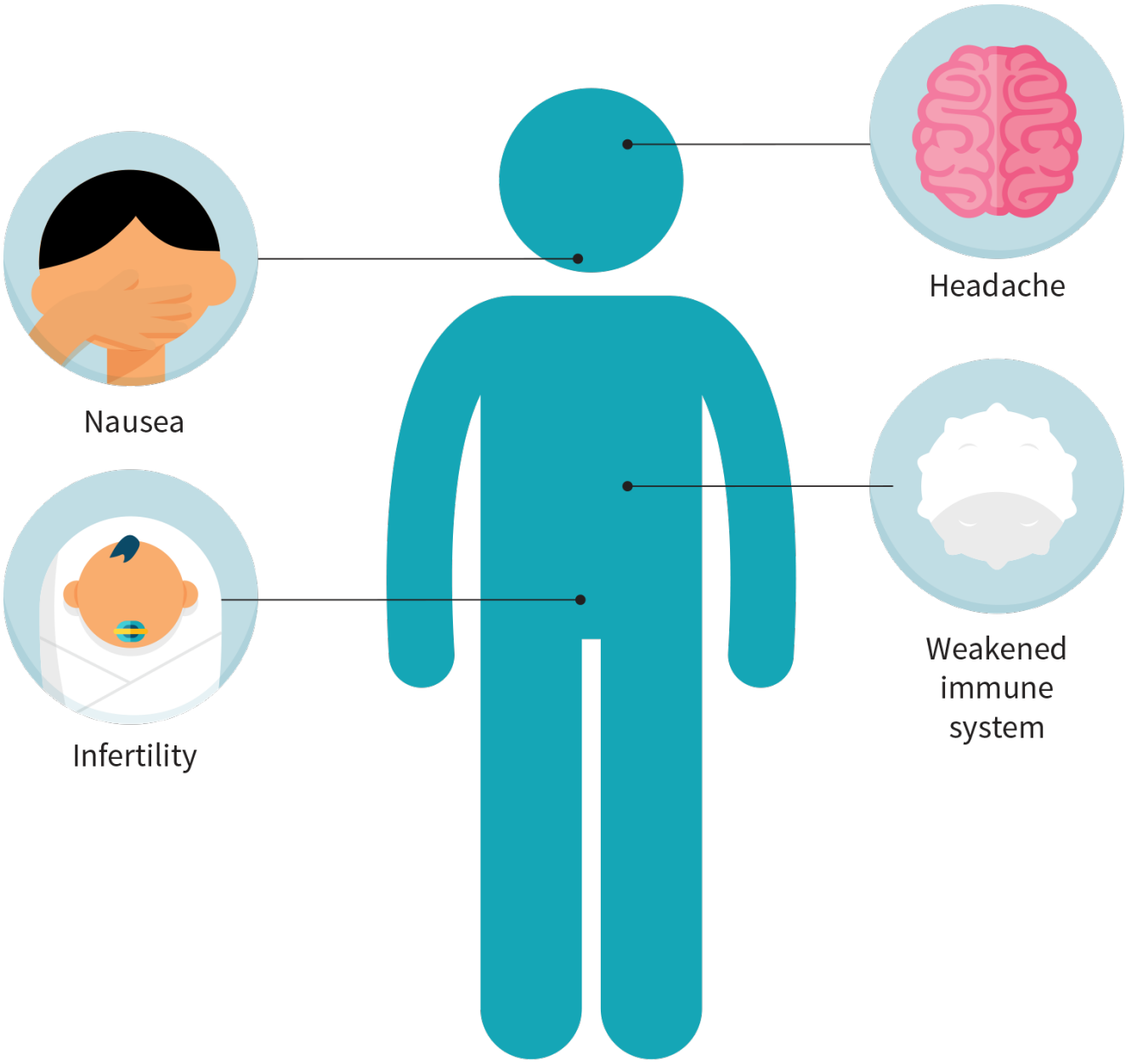
What makes *thunder god vine* an inadvisable supplement

> ⚠️ ***Caution:*** **This supplement has the potential to harm your health**
>
> Please read the following section carefully. The available evidence indicates that this supplement may have harmful effects. It should not be added to your supplement regimen.

Thunder god vine (*Tripterygium wilfordii*) is used in Traditional Chinese Medicine to treat a wide range of conditions. By decreasing the number of white blood cells, it reduces inflammation (and thus pain) around the joints, but it also makes the body more susceptible to infection, which can lead to sickness and potentially death.

Although *Tripterygium wilfordii* appears to be effective in treating rheumatoid arthritis, **it is not safe and should not be supplemented**.

Adverse effects of thunder god vine



The effective dose of this supplement is close to a harmful dose, which can cause a host of health issues

Much research has been conducted on *Tripterygium wilfordii* glycosides for rheumatoid arthritis, and it has been summarized in a meta-analysis of randomized controlled trials that investigated at the efficacy of *Tripterygium wilfordii* for rheumatoid arthritis.[177] Overall, 40 studies involving 3,092 participants were included, and a considerable reduction in morning stiffness, tender joints, swollen joints, and overall symptoms was found. A significant reduction in inflammation was identified, thus confirming its anti-inflammatory effects.

Although it's quite likely that *Tripterygium wilfordii* is effective, larger studies tended to find smaller (though still meaningful) effects. Although the authors didn't find evidence of publication bias and found that the average study was of fairly high quality by conventional standards, it's possible that the research still suffers from considerable bias, and future papers with more nuanced analyses based on study quality would be useful.

FAQ

Q. What about the supplements not covered in this guide?

Our guides are regularly updated, often with new supplements. We prioritize assessing (and reassessing) the most popular of them and those most likely to work. However, if there is a specific supplement you'd like to see covered in a future update, please let us know by filling out this survey.

Q. Can I add a supplement not covered in this guide to my combo?

Supplement with your current combo for a few weeks before attempting any change. Talk to your physician and research each potential addition. Check for known negative interactions with other supplements and pharmaceuticals in your current combo, but also for synergies. If two supplements are synergistic or additive in their effects, you might want to use lower doses of each.

Q. Can I modify the recommended doses?

If a supplement has a recommended dose range, stay within that range. If a supplement has a precise recommended dose, stay within 10% of that dose. Taking more than recommended could be counterproductive or even dangerous. Taking less could render the supplement ineffective, yet starting with half the regular dose could be prudent — especially if you know you tend to react strongly to supplements or pharmaceuticals.

Q. At what time should I take my supplements?

The answer is provided in the "How to take" section of a supplement entry whenever the evidence permits. Too often, however, the evidence is either mixed or absent. Starting with half the regular dose can help minimize the harm a supplement may cause when taken during the day (e.g., fatigue) or in the evening (e.g., insomnia).

Q. Should I take my supplements with or without food?

The answer is provided in the "How to take" section of a supplement entry whenever the evidence permits. Too often, however, the evidence is either mixed or absent. Besides, a supplement's digestion, absorption, and metabolism can be affected differently by different foods. Fat-soluble vitamins (A, D, E, K), for instance, are better absorbed with a small meal containing fat than with a large meal containing little to no fat.

Q. What are DRI, RDA, AI, and UL?

The Dietary Reference Intakes (DRIs) is a system of nutrition recommendations designed by the Institute of Medicine (a US institution now known as the Health and Medicine Division). RDA, AI, and UL are part of this system.

- Contrary to what the name suggests, a *Recommended Dietary Allowance* (RDA) doesn't represent an *ideal* amount; it represents the *minimum* you need in order to avoid deficiency-related health issues. More precisely, it represents an amount just large enough to meet the minimum requirements of 97.5% of healthy males and females over all ages — which implies that the RDA is too low for 2.5% of healthy people.
- The *Adequate Intake* (AI) is like the RDA, except that the number is more uncertain.
- The *Tolerable Upper Intake Level* (UL) is the maximum safe amount. More precisely, it is the maximum daily amount deemed to be safe for 97.5% of healthy males and females over all ages — which implies that the UL is too high for 2.5% of healthy people.

As a general rule, a healthy diet should include at least the RDA of each nutrient — but less than this nutrient's UL. This rule has many exceptions, though. For instance, people who sweat more need more salt (i.e., sodium), whereas people who take metformin (a diabetes medicine) need more vitamin B12.

Moreover, the DRIs are based on the median weight of adults and children in the United States. Everything else being equal (notably age, sex, and percentage of body fat), you likely need a lesser amount of nutrients if you weigh less, and vice versa if you weigh more. The numbers, however, are not proportional — if only because the brains of two people of very different weights have very similar needs. So you can't just double your RDIs for each nutrient if you weigh twice as much as the median adult of your age and sex (even if we overlook that people weighing the same can differ in many respects, notably body fat).

Q. What's the difference between osteoarthritis and rheumatoid arthritis?

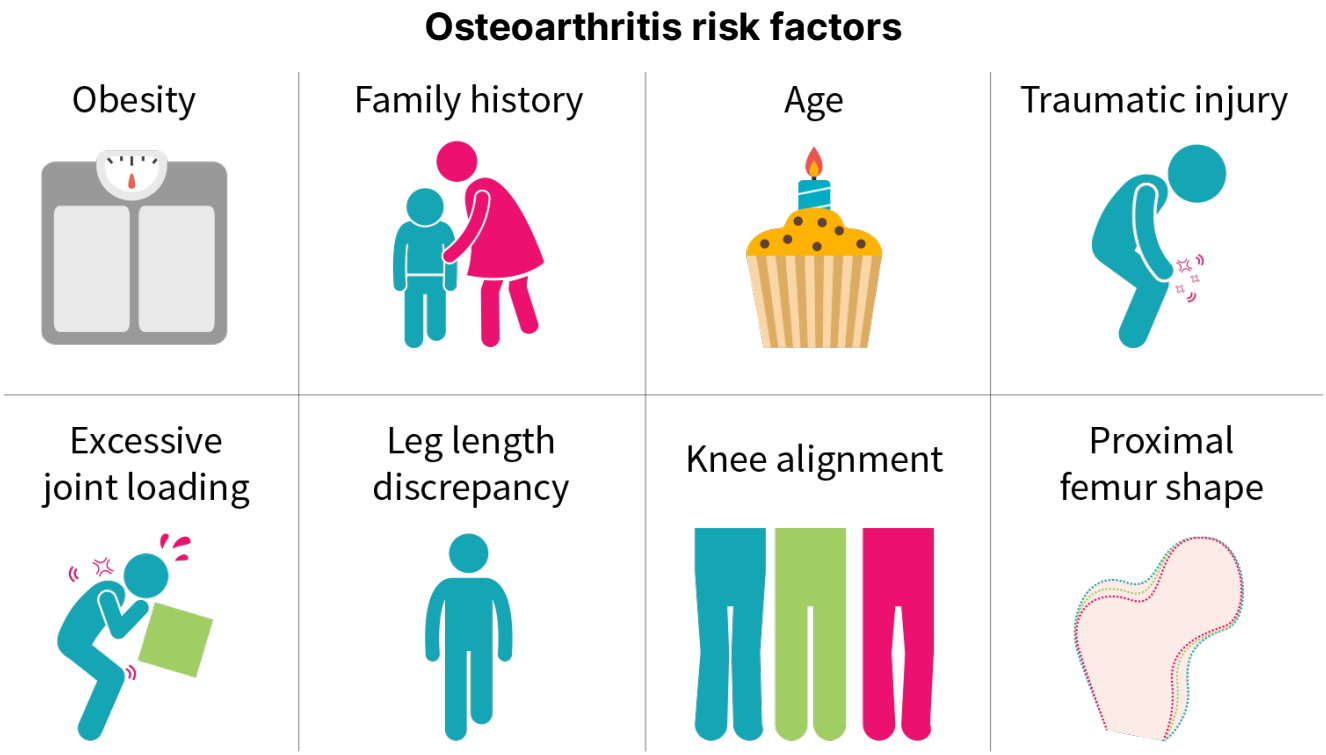
Osteoarthritis is caused by a progressive loss of cartilage that leads to joint inflammation via bone-on-bone rubbing, whereas rheumatoid arthritis is an autoimmune inflammatory disease that targets and degrades joint tissue.

Q. What are the risk factors for osteoarthritis?

Distinct risk factors for osteoarthritis, summarized below, include genetic susceptibility, morphological variations in bones and joints, traumatic joint injury, excessive joint stress, aging, and obesity.[178] Obesity is a major risk factor for osteoarthritis of the knee,[179] and weight loss can lead to improvements in the condition,[180] though more long-term studies are warranted.

Exercise can be useful for reducing pain and improving joint function,[181][182] though exercising with sore joints can be difficult, and not all forms of exercise are suitable for every patient.[183]

Pharmaceutically, treatment mostly revolves around the use of *nonsteroidal anti-inflammatories* (NSAIDs). While effective in reducing pain,[184] these drugs aren't without their adverse effects, which can include an increased risk of stroke and heart attack.[185][186]



Reference: Allen and Golightly. *Curr Opin Rheumatol.* 2015.[178]

Q. Will supplementing or consuming turmeric yield the same benefits as curcumin supplementation?

Curcumin is the active ingredient in turmeric that yields many of the benefits currently seen, but both are poorly absorbed in the gastrointestinal tract and usually require some enhancement to increase bioavailability.[187] Typically, a compound found in black pepper, known as piperine, is supplemented alongside curcumin to increase this bioavailability.[188] Other products increase bioavailability by using specialized formulations, such as the use of nanotechnology or a blend of essential oils.

It is unlikely, though, that simply consuming turmeric in small amounts through the diet will yield the same benefits as supplementing large doses of curcumin, due to the small dosage and poor bioavailability. It is also worth noting that turmeric has been found in some studies to be contaminated with heavy metals like lead.[189]

Q. What about essential nutrients? I don't see many in this guide.

It's plausible that some essential nutrients would be relevant to osteoarthritis, but evidence is sparse.

Calcium fructoborate, a form of boron, has shown potent reductions in circulating inflammatory cytokines associated with osteoarthritis in a handful of small trials,[190] and in osteoarthritis patients.[191] Although its impact on osteoarthritis-specific endpoints has yet to be studied in humans, at least one study in dogs suggests an improvement in physical function.[192]

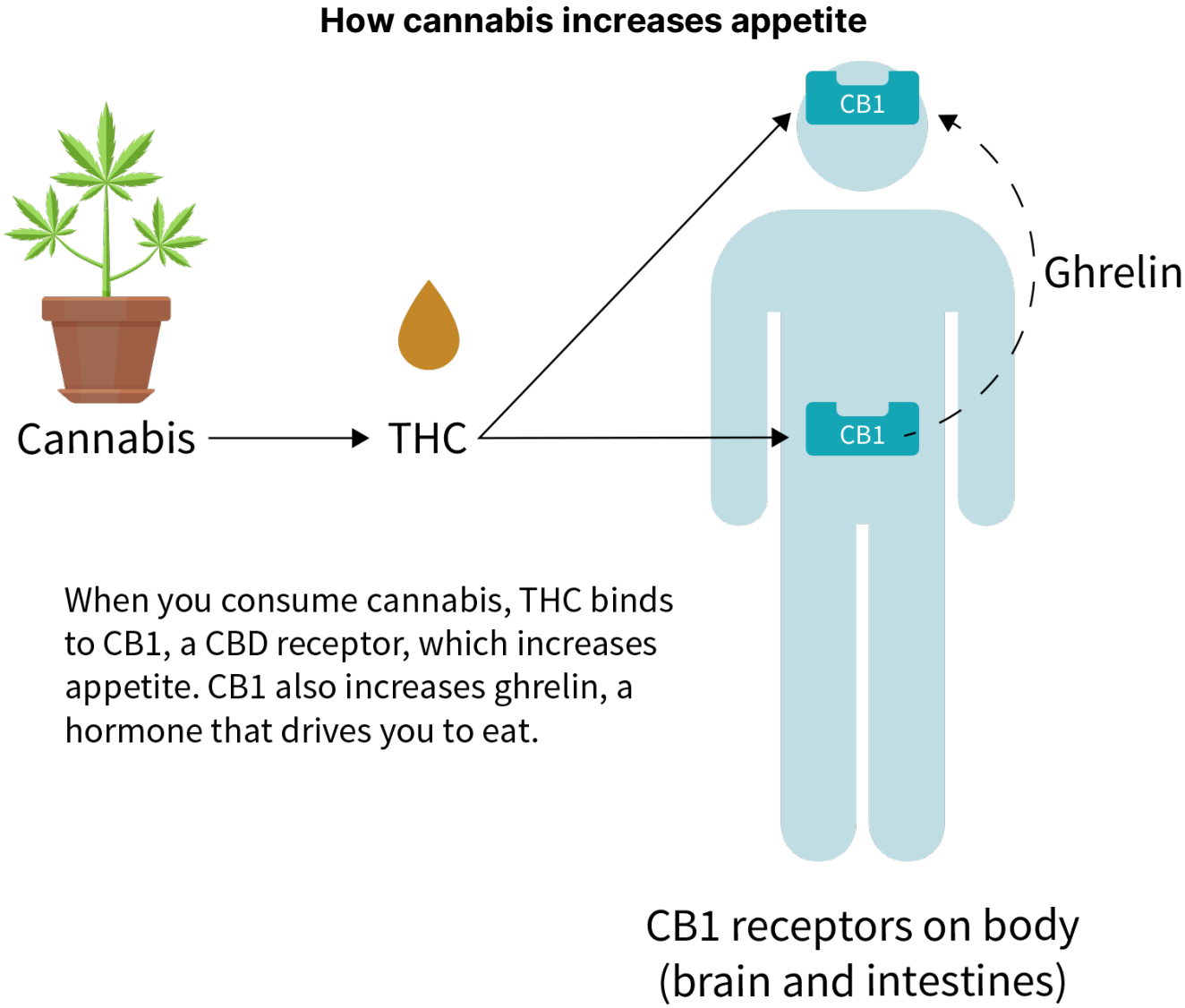
Vitamin K is also plausible[193], but not well-studied. It would be beneficial to see studies of common nutrient deficiencies in osteoarthritis and more trials on plausible supplements in the future, though there isn't very

much information at present.

Q. Will using CBD alone increase my appetite?

In short, probably not. THC, one of cannabis's main active ingredients, is primarily responsible for the appetite-stimulating effects of cannabis. THC can interact with receptors in the body that can, in turn, increase appetite. The method of consumption can affect how THC influences food choice and overall food intake, as can the amount and nature of the products consumed concurrently.

However, some products labeled “CBD only” or “0 THC” may still have high enough amounts of THC to cause an effect. Be conscious of who your source is if you chose to use CBD products.



References: Cota et al. *Int J Obes Relat Metab Disord*. 2003.[194] ● Patel and Cone. *Nature*. 2015.[195]

Q. What can I do to help prevent my fish oils from oxidizing?

Since fish oil is primarily polyunsaturated fat, it is prone to becoming rancid and oxidizing. Oxidation largely depends on exposure to heat, light, and oxygen. The addition of antioxidants to the final product can reduce the rate of oxidation during storage. Vitamin E is typically used, but there’s a lot of research on other

antioxidants like carnosic acid suggesting they might be superior.[196]

Part of the responsibility for ensuring fish oil remains unoxidized is on the buyer. Exposure of fish oil to light, heat, and oxygen accelerates the oxidation of the oil, with the magnitude of damage depending on the length and degree of exposure. Once you buy the supplement, it is prudent to store it in a cool place away from light, such as the fridge.

If you buy oil in a bottle, the bottle should be tinted to prevent light from getting through and small enough that you can work through it in a month or two. After all, oxygen gets in the bottle every time you open it. Some fish oil bottles come with a pump, which can help reduce oxygen exposure. Buying capsules instead of bottles can also help prevent oxidation.

Q. How do NSAIDs provide pain relief?

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to relieve pain or a fever. Common forms include aspirin (Advil), ibuprofen (Motrin), and naproxen (Aleve, Naprosyn) but they all work through a similar mechanism: they block an enzyme called *cyclooxygenase* (COX).[197] But there's a twist! This enzyme comes in two major forms: COX-1 and COX-2.

- *COX-1* is involved in the production of prostaglandins, which perform many functions in the body, including maintaining good kidney function and producing the protective layer of the gastrointestinal (GI) tract.
- *COX-2* produces molecules responsible for pain and inflammation, so that's the one to target if you want to reduce these effects.

Most NSAIDs nonselectively target both COXs, which explains their infamous GI adverse effects. However, the NSAID celecoxib (Celebrex) binds more to COX-2 than COX-1, so it can target pain and inflammation with fewer adverse effects, at least in theory. In reality, the advantages of celecoxib are not so clear-cut. A recent review found that the relative harm and benefit of celecoxib for people with osteoarthritis are hard to assess, partially because of the general scarcity and possible bias of evidence due to industry involvement.[198]

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