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Natural Solutions

4 Natural Supplements & How They Work

Genetic Lifehacks
Learn. Experiment. Optimize.

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Introduction

Did you know that your genes interact with the foods you eat, medications you take, and supplements that you consume? The way that you react to a supplement may be different than other people. Moreover, you may not get the same benefits from a supplement due to genetics.

Quality information about natural supplements can be hard to find. Many articles just regurgitate the same surface-level information. Some websites are obviously cherry picking research in order to sell you a product.

This eBook covers four popular supplements, with a focus on the clinical trials and quality research studies. References are linked right in the paragraphs, so you can check out the peer-reviewed publications yourself.

Disclaimer: The supplement research covered here is for informational and educational purposes only. Talk with your medical provider for medical advice. Supplements are not regulated by the FDA.

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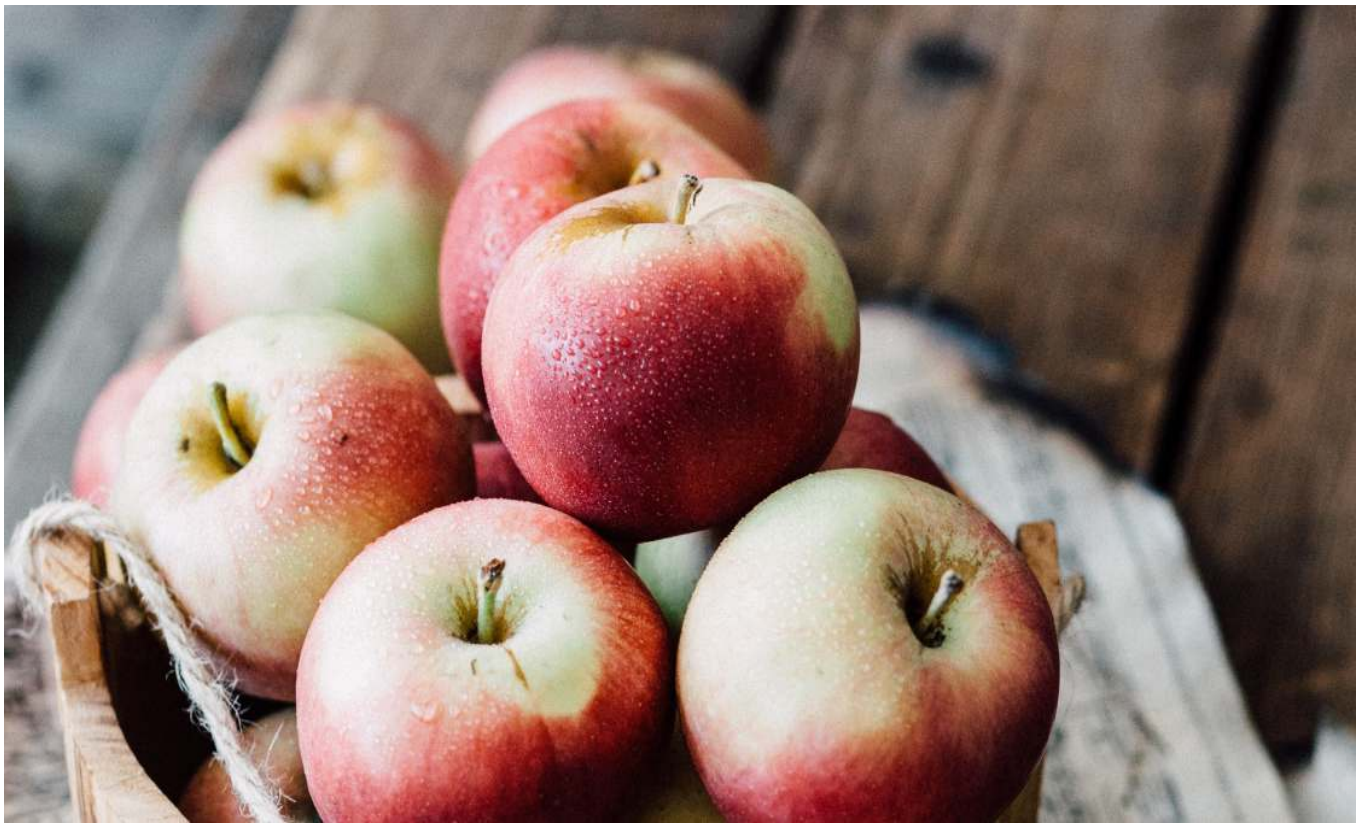
Quercetin: Scientific studies + genetic connections

Quercetin is a natural flavonoid acting as both an antioxidant and anti-inflammatory. This potent flavonoid is found in low levels in many fruits and vegetables, including elderberry, apples, and onions.

As a supplement, quercetin has many positive health benefits. This article focuses on the results of clinical trials involving quercetin as well as linking to specific genetic topics. By using your genetic data, you can make a more informed decision on whether quercetin is worth trying.



Quercetin Research:

Quercetin has been shown in cell studies to be a fabulous, wonder-supplement for many different conditions. You may have read about how great it is on Facebook or other websites.

But… the studies in humans don't always match up with the cell studies and animal studies. I'm going to focus mainly on the results of human trials of quercetin and dive into cell studies just for the genetic links.

Food sources of quercetin:

Quercetin is a flavonol found at low levels in a lot of different fruits and vegetables. Here is a list of foods with a higher quercetin content (from Phenol-explorer and the USDA).

- Capers: 234mg/100g
- Black elderberry: 42 mg/100g
- Dark chocolate: 25 mg/100g
- Shallots and onions: 10 – 31mg/100g
- Apples, with skin: 2 -4 mg/100g
- Bilberry: 1.27/100g
- Red Wine: 0.83 mg/100 ml
- Apple juice: 0.48 mg/ 100ml

Blood pressure reduction studies that use quercetin:

In a double-blind, randomized placebo-controlled study, quercetin reduced blood pressure in men with hypertension. The study used 730 mg/day of quercetin and found that it reduced systolic blood pressure by 7 mmHg and diastolic blood pressure by 5 mmHg.[ref]

Another study using a smaller dosage of quercetin had a smaller decrease in blood pressure. The study results showed a decrease in systolic blood pressure of 3.6 mmHg in overweight patients with high blood pressure using only 162 mg/day of quercetin.[ref]

A meta-analysis that combined the data from 7 clinical trials found a significant reduction in blood pressure in randomized controlled trials that used doses of more than 500mg/day.[ref]

Quercetin for oxidative stress and oxidized LDL:

When a cell has an imbalance of reactive oxygen species (ROS) to antioxidants, it is called oxidative stress. These reactive oxygen species contain an unstable balance of electrons and can cause reactions that damage the cell. Too much oxidative stress can cause DNA damage, the production of inflammatory signals, and eventually cell death.

Quercetin is a free radical scavenger shown in studies to help prevent oxidized cholesterol.[ref] This is important because oxidized cholesterol may accelerate atherosclerosis or plaque build-up in the arteries.[ref]

A double-blinded, placebo-controlled cross-over trial in overweight adults with metabolic syndrome found that 150mg/day of quercetin decreased the concentration of oxidized LDL cholesterol. There wasn't much of an effect on any other health markers at this dosage, but just decreasing the oxidized LDL should reduce the risk of cardiovascular disease.[ref]

Researchers theorize that oxidative stress contributes to Alzheimer's disease pathology. Animal and cell studies show that quercetin can protect against oxidative stress in the brain and partially prevent the associated neuronal toxicity.[ref]

Related article: APOE and Alzheimer's Risk

Most of the time, preventing oxidative stress is something you want to do – but not always. One of the benefits of exercise is to create stress, which causes cells to respond by adapting and producing more mitochondria. Quercetin's effect on exercise performance has been researched. The results of the studies have varied, but most show that quercetin doesn't increase exercise performance.[ref] If you are supplementing with quercetin, consider whether you should take it at a time that it won't interfere with the benefits of exercise-induced stress.

Related article: Athletic Performance Genes

Quercetin as a senolytic (longevity benefits):

Cellular senescence occurs when a cell can no longer divide or function normally. Basically, the cell just sits there, giving off pro-inflammatory signals. Those inflammatory factors can then impact the surrounding cells. Kind of like a drug dealer moving into the neighborhood… bringing down the whole area.

The body can get rid of senescent cells pretty well – up to a point. But when too many senescent cells accumulate, things start going downhill. Recent research points to senescent cells actually causing a lot of the diseases of aging, rather than just being a symptom of aging.

Clearing out senescent cells could either delay or possibly reverse aging. *That would be pretty cool…*

Quercetin has been studied recently as a senolytic – a way of clearing out senescent cells. Animal and cell studies are promising.[ref][ref]

But what about human trials? When quercetin is combined with Dasatinib (a leukemia drug), it clearly reduces senescent cells.[ref][ref] This is an exciting field of study that shows a lot of promise for the future.

One more way that quercetin may improve atherosclerosis and oxidized LDL is by reducing senescent cells in the endothelium (lining of the arteries). A new study looked at quercetin's effect on a cell model of atherosclerosis. The study found that quercetin inhibited the foam cells created by oxidized LDL in atherosclerosis, and it also decreased senescent cells. While just a cell study, this points to quercetin possibly having multiple beneficial effects on cardiovascular disease.[ref]

Related article: NAD+, nicotinamide riboside, and NMN

Advanced glycation end products:

The production of advanced glycation end products (AGEs) in the body (and through foods we eat) increases the diseases of aging. For AGEs that are produced in the body, methylglyoxal levels are important.

A randomized, double-blind, placebo-controlled crossover trial found that 160 mg/d of quercetin reduced methylglyoxal, a precursor for AGEs, by an average of 11% after four weeks.[ref]

Related article: Advanced Glycation End Products and your genes

Uric acid:

High uric acid levels are a risk factor for gout. A double-blind, placebo-controlled cross-over trial in healthy men with higher uric acid found that quercetin lowered uric acid levels. The trial used 500mg/day of quercetin for four weeks and decreased uric acid by 26·5 μmol/l on average.[ref]

Rheumatoid Arthritis:

Since quercetin can reduce both pain and inflammation, it makes sense that it could help with rheumatoid arthritis. Indeed, a two-month placebo-controlled trial found that quercetin reduced morning pain, stiffness, and post-activity pain. Quercetin also reduced TNF-alpha (inflammatory cytokine) levels. The trial included 50 women with RA who took either 500mg/day of quercetin or a placebo.[ref]

Related article: TNF-alpha and rheumatoid arthritis

Immune boosting:

A randomized placebo-controlled trial found that 12 weeks of quercetin at 1000mg/day reduced upper respiratory tract infections.[ref]

Excessive exercise can make you more susceptible to getting sick. In a mouse trial where the mice exercised to fatigue (treadmill) for days, researchers found that quercetin offsets the increased propensity to get sick after exercising to fatigue.[ref] This may be something to try if you are training for an upcoming exercise-intensive event.

A human study showed that quercetin was safe (>5g/day) and effective for some people in reducing the viral load in hepatitis C patients.[ref]

Mast Cell Blocker:

Mast cells are an important part of the immune system that can degranulate and signal for an inflammatory response. Overactive mast cells can be a problem, leading to allergic responses or to mast cell activation syndrome. One compound that mast cells can release is histamine.

Quercetin stabilizes mast cells and inhibits the release of histamine.[ref]

Related article: Mast Cell Activation Syndrome Genes

Caffeine and quercetin (CYP1A2 gene):

Quercetin inhibits CYP1A2, which is the enzyme the body uses to metabolize caffeine. [ref] If you are a slow metabolizer of caffeine, quercetin along with caffeine, may mean that you feel the effects of caffeine for a longer period of time.

Related article: CYP1A2 Variants

Absorption, transport, and metabolism of Quercetin

Any substance that affects the body needs to be absorbed (usually in the intestines), transported throughout the body, and broken down and eliminated (usually through the liver). One big difference between cell studies and *in vitro* human studies is the absorption and metabolism of substances.

Absorption of quercetin:

A study found that the bioavailability of quercetin in humans is about 45%. The half-life of quercetin ranges between 11-28 hours, so taking it daily will build up more than just what was consumed that day.[ref]

Researchers have looked at the interaction between different types of foods and the absorption of quercetin. They found that eating a meal containing fat and the quercetin supplement can increase bioavailability.[ref] Alternatively, if you usually take a fish oil supplement, you may want to take it simultaneously with your quercetin.

Transdermal absorption of quercetin is an interesting idea, especially with the antioxidant properties and the possibility of enhancing the skin. Since it is hydrophobic, quercetin won't dissolve well in water. One study found olive oil and soybean oils were better for transdermal absorption, compared to avocado, raspberry seed, and coconut oils.[ref] Another study used solid lipid nanoparticles with quercetin to enhance skin absorption.[ref] (Personal note...quercetin is a yellow-ish powder that stains everything it touches. When mixed with olive oil, it lends a jaundiced-hue to skin.)

Metabolism and interactions:

Quercetin is an inhibitor of the CYP2C8 enzyme. If you have genetic variants that slow down the CYP2C8 variant and stack quercetin with a medication that uses that enzyme, you could majorly impair the metabolism of the medicine.

Check your genetic data for CYP2C8 Genetic Variants

Quercetin has a catechol structure and is partly metabolized through the COMT enzyme. If you carry the slower version of COMT, you may want to be careful and not go overboard with quercetin.

> Check your genetic data for COMT variants

Transport of quercetin:

The MATE1 (multidrug and toxic compound extrusion transporter-1) protein is the quercetin transporter. It is coded for by the SLC47A1 gene.[ref]

What quercetin doesn't do...

I don't want to leave you with the impression that quercetin is a miracle cure for everything. Far from it! Instead, it may be another tool for a specific purpose at the proper dosage.

For example, a trial of 162 mg/d of quercetin for six weeks showed little effect on C-reactive protein, leptin levels, or blood glucose levels in overweight adults with metabolic syndrome. The study did show that the 162 mg dose was safe.[ref]

Another study in healthy adult women found no significant effect from either 500 mg/day or 1000 mg/day on inflammatory markers and immune function.[ref]

The studies that show more of an effect seem to be using higher dosages (500-1,000 mg/day). Plus, it may be more effective in people who have a problem (e.g., high blood pressure or cholesterol) rather than having a large effect on healthy people.

Where to get quercetin:

You can get quercetin as a supplement in capsules or as a powder. The advantage of getting it as a powder and either putting it in a smoothie or into capsules yourself is that you can eliminate the excipients in most capsule formulas. The drawback to the powdered form is that it is yellow and will stain everything that it touches a bright yellow. The stains do eventually come out of kitchen towels... lessons learned.

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Luteolin: Antihistamine, Memory, and Brain Fog

Luteolin is a flavonoid found in fruits, vegetables, and herbs. It possesses a variety of anti-inflammatory, antihistamine, and antibacterial properties, according to research studies. Furthermore, it is neuroprotective, bringing benefits to the brain for memory, brain fog, and possibly protecting against neurodegenerative diseases.

In this article, I dive into the research studies on luteolin, explaining the clinical trials and examining the animal research on how it works. I'll also explain how it is absorbed and how it interacts with genetic variants, such as COMT.

Luteolin: Where to get it and what research studies show

Luteolin is a flavonoid found in small amounts in several herbs and vegetables. Plants produce flavonoids, such as luteolin, as a cellular defense against pathogens or UV radiation. Many of these plant molecules also bring health benefits to us when we consume them.[ref]

Luteolin foods: Parsley, carrots, artichokes, celery, thyme, chamomile tea, olive oil, oranges, and oregano contain the flavone luteolin.

Luteolin vs. lutein: Luteolin is not to be confused with lutein, a plant pigment that can help with macular degeneration.

Luteolin as an antihistamine and mast cell stabilizer:

Research shows that luteolin can act as a **mast cell stabilizer and reduce histamine release.**[ref][ref] This may benefit anyone dealing with mast cell activation syndrome (MCAS) or histamine intolerance.

Brain Fog in MCAS: The 'brain fog' term applies to the inability to think clearly or concentrate. According to some researchers, inflammation and histamine release cause brain fog. They believe that luteolin can help with brain fog, citing studies that show it can improve focus in children with autism.[ref].

Related article: Brain Fog and Genetics

Neuroprotective effects of luteolin:

Research shows that luteolin may have clinically meaningful neuroprotective effects. This is important since a lot of research studies only show very minor benefits that aren't really meaningful.

Brain fog: Studies show that luteolin may help with cognitive dysfunction caused by inflammation. Luteolin decreases the cytokines that cause inflammation in the brain. [ref] Other research explains that luteolin may help specifically with "brain fog" by decreasing neuroinflammation.[ref]

Long Covid: Some researchers think that luteolin may help with brain fog, or cognitive issues, in long Covid.[ref] The mechanism of how luteolin could help seems logical, but there aren't any clinical trials on luteolin for Long Covid (yet).

Neurodegenerative diseases such as Alzheimer's: The creation of amyloid-beta, which builds up in plaques in Alzheimer's sufferers' brains, requires the O-glycosylation of the amyloid precursor protein. Inhibiting this process could reduce amyloid in the brain, at least in theory. Let me be clear: this is purely theoretical and has not been confirmed in human investigations.

- Luteolin selectively **inhibits the type of O-glycosylation** (Mucin-type *O*-glycosylation) involved in the formation of **amyloid-β**.[ref]
- Animal studies show luteolin **inhibits neuroinflammation** by controlling microglia activation.[ref]
- In a mouse study of Alzheimer's, luteolin protects against amyloid β memory dysfunction and also increases levels of endogenous antioxidants, including Mn-SOD, Cu/Zn-SOD, and glutathione.

Keep in mind that mouse and cell studies don't always pan out when it comes to Alzheimer's research… but for luteolin, there is little risk and a lot of potential benefits.

Luteolin as an anti-inflammatory:

Research also shows that luteolin may help with chronic inflammation.

- In cell studies, luteolin i**nhibits TNF-alpha and IL-6** released via **suppressing NF-κB**.[ref] TNF-alpha and IL-6 are linked to many chronic diseases caused by elevated inflammatory cytokines.
- In other research, luteolin reduces **IL-6** (interleukin 6), an inflammatory cytokine produced in response to bacterial infections.[ref]
- In microglial cells, luteolin and another flavonoid, apigenin, suppress **IL-31 and IL-33**.[ref] IL-31 is an inflammatory cytokine produced by activated T lymphocytes, and it plays a role in **chronic inflammatory diseases**.

All in all, the research shows luteolin as a specific anti-inflammatory to target elevated TNF, IL-6, IL-31, and IL-33.

Luteolin and sleep:

Animal studies show that luteolin has a sleep-inducing effect – at least when given with a sleep drug.

Interestingly, this hypnotic effect was driven by interactions with the **adenosine receptor.** The build-up of adenosine and its binding with the adenosine receptor drives us to need to sleep each night, so the interaction with the adenosine receptor theoretically would only increase sleepiness at the end of the day (not making you sleepy during the day). Additionally, the research showed that **luteolin increased sleep time and non-REM** sleep.[ref]

Luteolin as an antimicrobial:

Cell studies show that luteolin acts as an antimicrobial agent against several common bacterial and viral pathogens.

- It stops the growth of *Staphylococcus aureus* **(staph infection).**[ref]
- Luteolin acts as an antiviral agent against one of the causes of encephalitis (Flaviviridae virus).[ref]
- In trials for **SARS-CoV-1,** luteolin blocks viral entry into host cells. Some researchers theorize it may also be helpful for SARS-CoV-2, but clinical trials are needed.[ref]
- Cell studies also show that luteolin has antiviral activity against the **flu virus (H1N1**).[ref]

Luteolin inhibits cell proliferation in cancer:

First and foremost, let me emphasize that I am not advocating for anyone to self-treat cancer with supplements. Instead, this research summary provides broad cancer prevention advice.

In epidemiological research, eating fruits and vegetables has been linked to lower cancer risk. However, epidemiological studies that ask people what they eat and then associate that with an outcome are really just vague pointers towards a possible link. Perhaps people who naturally eat many vegetables are also likely to have genetic variants in their taste receptors. It is possible these variants could also impact cancer risk.

Multiple studies have shown that luteolin induces **apoptosis** (cell death) in cancer cells in vitro. It also causes cell cycle arrest, which prevents cancer cells from replicating. Studies show that luteolin inhibits cancer cell proliferation in two ways: by blocking the IGF1 receptor and by acting on GSK-3. Recent studies also show that luteolin downregulates mTOR and upregulates P53 (tumor suppressor gene).[ref][ref][ref][ref]

While it is excellent that luteolin works to stop many different types of cancer cells from proliferating in a petri dish, the question remains whether this works at obtainable levels in real life. In other words, can you take enough supplemental luteolin to actually make a difference – without side effects? It is a question that needs clinical trials for answers.

What about just eating foods rich in flavonoids? A trial looking at cancer prevention from consuming flavonoid-rich vegetables, including luteolin content, found no difference in cancer risk among women who consumed the most flavonoids compared to the least.[ref]

Luteolin for skin health and sunburns:

A clinical trial found that a nanoparticle formula containing a luteolin-rich plant extract decreased UVB-induced erythema (e.g., sunburns). The formula seemed to work when applied before UVB exposure and, to some extent, after exposure. After exposure, the luteolin-rich plant extract was as effective as the hydrocortisone cream.[ref]

Luteolin in cholesterol levels:

There is a ton of research on cholesterol, and much of it seems contradictory — what is the right amount? Instead of looking only at total cholesterol or just LDL cholesterol, researchers are now dialing in the specific types of cholesterol-related lipid particles.

In general, apoB-containing lipoproteins, such as LDL and chylomicron remnants, link to plaque buildup in the arteries (not good).[ref] Luteolin acts on HNF4α, a nuclear transcription factor, in regulating the secretion of apolipoprotein B (apo B) containing lipoproteins.[ref] This means that luteolin is acting upstream of the production of cholesterol in the liver — regulating the production of cholesterol.

Gut Microbiome:

The gut microbiome and intestinal barrier integrity are essential in preventing fatty liver disease (NAFLD).

Luteolin protects against fatty liver by improving the intestinal barrier integrity. It also increases microbial diversity in the gut, according to animal studies.[ref]

Related article: NAFLD and genetics

Absorption, Side Effects, and Metabolism of luteolin:

Luteolin can be absorbed orally and then show up in the bloodstream after an hour to an hour and a half.[ref]

- It has a half-life of 5-7 hours.[ref]
- It is broken down and then eliminated in bile (through feces).[ref]
- Luteolin can also be absorbed transdermally because it is a relatively small molecule.

Liposomal luteolin: Studies on colon cancer cells show that liposomal luteolin is much more effective than free luteolin.[ref] Liposomal formulations include fatty acids along with luteolin which aids in intestinal absorption.

Stack with fat: If you take a powdered supplement, you may find that it is absorbed better when you take it along with fat (meal containing fat, fish oil pills, a glass of whole milk — you get the picture).

Genetic Interactions

Luteolin is metabolized using the COMT enzyme. People with low COMT production, due to the genetic variants below, may want to be cautious with high doses of luteolin. Watch for mood swings or irritability as side effects since COMT also helps to regulate neurotransmitter levels. Additionally, be careful if stacking luteolin with other medications or supplements that utilize the COMT enzyme for metabolism.

Drug interactions? A study investigating luteolin showed that it doesn't interfere with the main enzymes utilized in drug metabolism at normal human consumption levels. [ref] At high levels, luteolin may inhibit CYP2B6, CYP2C9, and CYP2D6.[ref] Talk with your doctor or pharmacist for any questions about interactions with medications you currently take.

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L-theanine for anxiety: genetics and nature's chill pill

A popular supplement for anxiety, l-theanine from green tea is often promoted as a miracle solution for mood and sleep.

This article examines the research and clinical trials on l-theanine, explaining how it works and the likely effects of supplementation.

What is l-theanine?

L-theanine is an amino acid with a similar chemical structure to glutamate, which is a neurotransmitter. It is found in green tea and mushrooms, and l-theanine is readily available as a supplement.

People often take l-theanine supplements for anxiety, and studies do back up this claim somewhat. But l-theanine is more than just a 'chill pill', as you will see from the research on inflammation and brain health.

In tea, l-theanine makes up about 1 -2% of the dry weight of the leaves. It is true for both black and green teas, with different tea varieties containing different amounts. [ref]

On average, a cup of tea contains about 25mg of l-theanine. Interestingly, l-theanine takes away some of the bitter taste of caffeine through binding to the taste receptors for umami, a savory taste.[ref]

In the brain, l-theanine binds to glutamate receptors. But l-theanine doesn't have as strong an affinity to the receptor as glutamate, so it doesn't replace it entirely. Instead, it somewhat inhibits glutamate reuptake and increases brain levels of GABA.[ref] GABA acts as an inhibitory neurotransmitter, putting the brakes on brain excitement.

Recent research also shows that l-theanine binds to cannabinoid receptor 1 (CB1). This competitive binding then inhibits the CB1 receptor.[ref]

Studies on l-theanine for anxiety:

L-theanine has been tested in clinical trials for anxiety. Let's take a look at some of the results:

A 2006 cross-over trial found that l-theanine reduced heart rate and stress response molecules in response to acute stress tasks. The heart rate variability results showed that the reduction in heart rate was "attributable to an attenuation of sympathetic nervous activation."[ref]

A randomized, placebo-controlled, cross-over, and double-blind trial looked at the effects of 200mg/d of l-theanine on adults with no mood issues. The results showed a decrease in depression and anxiety traits as well as better sleep. Cognitive function, executive function, and verbal fluency all improved.[ref]

On the other hand, an 8-week trial in people with Generalized Anxiety Disorder found that l-theanine did not reduce anxiety.[ref]

Researchers looked at different doses of l-theanine and measured the startle response. [ref] Doses of 200-400 mg did decrease the startle response, but at doses over 400 mg, there was no additional benefit.

Related article: Inflammation genes and anxiety

How does l-theanine stack up against benzos?

A clinical trial looked at the anxiety reduction from 200 mg of l-theanine vs. alprazolam (benzodiazepine) or a placebo. The study results showed that l-theanine helped with relaxation during non-stress conditions, but neither then alprazolam nor l-theanine had acute anxiety-reducing effects during anticipatory anxiety.[ref] To me, the difference between anticipatory stress and a suddenly anxious situation is similar to dreading a final exam for a week vs. having a pop-quiz.

Studies on l-theanine for depression:

Surprisingly, there isn't a lot of published research on l-theanine for depression. Anxiety and depression often go hand-in-hand, so I expected to find more research on the combination.

A clinical trial using 250mg/day of l-theanine in adults with major depressive disorder showed that anxiety traits improved. Sleep disturbances were helped by the l-theanine also.[ref]

Sleep studies with l-theanine:

It would make sense that something that can decrease anxiety would help people who have sleep problems due to constantly worrying about things all night. Plus, supplement sellers of l-theanine often promote its use for sleep. But, to be honest, the research on the topic is slim.

- A randomized, double-blind, placebo-controlled trial using 100 mg of l-theanine 4x per day in boys with ADHD showed some improvements in sleep quality.[ref]
- Additionally, the clinical trial mentioned above for stress-related symptoms also noted improved sleep quality scores in participants taking l-theanine.[ref]

Will it give you nightmares? An animal study showed that GABA plus l-theanine effectively decreased the time it took to fall asleep and the time spent sleeping. It also almost doubled the time spent in REM sleep.[ref] I mention this animal study because some people report that l-theanine causes vivid dreams for them, which may go along with changes in REM sleep.

Caffeine plus l-theanine: taking the edge off

One benefit of l-theanine is to take the edge off the caffeine jitters.

A clinical trial showed that combining l-theanine with caffeine eliminated the negative effects of caffeine in people who weren't used to drinking it.[ref]

Another study found that moderate levels of l-theanine and caffeine improved accuracy and alertness in participants.[ref]

A double-blind, placebo-controlled study found that 100mg of l-theanine plus 50mg of caffeine increased vigilance and decreased errors during a sustained attention task. In other words, it increased the participants' ability to focus.[ref]

Interestingly, caffeine jitters are something that happens based on genetic variants in the ADORA2A gene. Thus, if you naturally don't feel anxious, then theanine may not have much of an impact as far as a combo with caffeine.

> Check your ADORA2A genetic data here.

Targeting inflammation and the immune system:

Animal studies show that l-theanine decreases TNF-alpha levels and increases the anti-inflammatory cytokine IL-10.[ref]

Psoriasis is a skin inflammatory disease that involves an increased immune cell response in the epidermis. Studies show that l-theanine reduces the overactive inflammatory response by **inhibiting IL-23,** an inflammatory cytokine. The animal study also indicates that l-theanine regulates other inflammatory pathways, including **IL-17A and NF-κB**.[ref]

T cells are one of the body's first lines of defense against microbial pathogens. Supplementing with l-theanine has been shown to prime a specific subset of T cells, called gamma-delta T lymphocytes. It may be why supplementing with l-theanine decreases cold and flu symptoms.[ref]

Brain health:

Animal studies show that l-theanine stimulates the growth of neural progenitor cells. Essentially, l-theanine inhibits glutamine uptake without affecting glutamic acid uptake. It stimulates an increase in SLCC38A1, which is the glutamine transporter. The overexpression of SLC38A1 facilitates the pathways required for neurogenesis.[ref]

Cell studies using neuronal cells show that the upregulation of SLC38A1 by l-theanine promotes the generation of new neurons.[ref]

Promoting neurogenesis may be why studies in older adults who drink green tea with high theanine concentration have less cognitive decline than typically seen in aging.[ref]

L-theanine in aging:

Animal studies show that l-theanine may help to delay neurodegenerative diseases. The research shows that l-theanine activates SIRT1 and inhibits nuclear factor-κB (NF-kB), both of which should be beneficial in aging through reducing the expression of inflammatory factors.[ref]

Absorption, transport, and dosage:

L-theanine dosage for anxiety:

The average cup of tea is around 20 to 25mg of l-theanine. Someone drinking multiple cups of tea in a day could be getting 100+ mg of theanine.

Clinical trials above used doses in the range of 100 to 900 mg/day without negative effects. There doesn't seem to be evidence, though, that the higher doses are more effective. Some trials split the dosage into several 100 mg capsules over the course of the day. It makes sense when you look at the short half-life of l-theanine.

Absorption in the gut:

For any supplement pill or medication capsule to work in the body, it needs to be absorbed in the intestines, moved into the bloodstream, and taken up into cells. Along the way, many substances are broken down or metabolized by the liver or other enzymes so the body can eliminate them.

- Both l-theanine in capsules and l-theanine in green tea are readily absorbed, with peak plasma values observed after 45 minutes.[ref]
- The addition of piperine increases the absorption of l-theanine.[ref]
- The half-life of l-theanine is about an hour to an hour and 15 minutes. Meaning l-theanine is absorbed and metabolized relatively quickly. It does cross the blood-brain barrier and is detectable in the brain about a half hour after oral administration.[ref]

Transport into the cell: A transporter protein is needed to move l-theanine into a cell. Research shows that the LAT1 transporter, which moves several amino acids into cells, including l-leucine, is utilized by l-theanine.[ref]

L-theanine's uptake is inhibited by l-leucine, a branch chain amino acid found in many proteins, including milk. Thus, to increase your ability to absorb l-theanine, drink your green tea without milk and away from branch-chain amino acid protein drinks.

SLC7A5 gene: encodes the LAT1 transporter, which transports l-theanine into cells. [ref]

Studies don't directly investigate the impact of the LAT1 variant on l-theanine, but the variant below does increase expression of the transporter and impacts levels of transport in other drugs.

Check your genetic data for **rs4240803** (23andMe v4, v5):

- A/A: increased expression[ref][ref]
- A/G: increased expression
- G/G: typical

Theanine levels in different types of tea:

The amount of l-theanine varies quite a bit by the type of tea.

Commercial name	/1 g tea leaves (mg)		$m_{caffeine}/m_{L\text{-}theanine}$	Type
	$m_{L\text{-}theanine}$	$m_{caffeine}$		
Mao Feng White	9.11	15.38	1.69	White
Pickwick White	7.00	17.94	2.56	
China Pai Mu Tan	5.67	18.22	3.21	
ChinaYunnan White	3.24	15.62	4.82	
Tanzania Black	6.75	13.48	2.00	Black
English morning	5.09	19.44	3.82	
Assam Harmutty	5.69	19.93	3.50	
Russian Samovar	3.80	16.13	4.24	
Ceylon OP Highrown	4.33	14.61	3.37	
Earl Grey	2.70	16.48	6.10	
Twinings Earl Grey	2.47	16.61	6.72	
Lord Nelson Earl Grey	10.85	23.44	2.16	
Lipton Earl Grey	5.65	21.44	3.79	
Lipton Earl Grey Lemon	7.83	23.22	2.97	
Darjeeling First Flush Leaf Blend	4.25	14.10	3.32	
Darjeeling Happy Valley	2.09	14.40	6.89	
Korean Green	10.93	17.36	1.59	Green
ChinaYunnan FOP	10.88	17.05	1.57	
Mao Feng Green	8.53	13.48	1.58	
Vietnamese Green	10.11	16.95	1.68	
China-Chun Me	6.11	14.97	2.45	
Japanese Kokaicha	4.70	11.47	2.44	
China Gunpowder	3.83	13.07	3.41	
China OP Sencha	2.92	11.32	3.88	
Green Earl Gray	2.65	10.23	3.86	
Pickwick Green Cranberry	4.40	14.89	3.38	
PickwickGreen Melon	4.76	20.11	4.22	
Mr Perkins Green Peach	7.79	19.72	2.53	
H Green Mint	6.71	21.97	3.27	
H Green Lemongrass	6.76	22.75	3.37	
Lipton Green Nature	7.30	18.85	2.58	
Japanese Bancha	2.81	11.82	4.21	
Oolong	0.90	8.01	8.90	Oolong
Tradition	9.78	26.15	2.67	
Hwa Gung	12.37	39.71	3.21	
Alishan	3.18	10.96	3.45	
King's	4.21	11.72	2.78	
China Yunnan Pu-Erh	0.00	12.59	-	Pu-erh

OP: Orange pekoe; FOP: flowery orange pekoe; these are the names of different tea leaf grades

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Conclusion:

Tea is one of the most popular beverages consumed worldwide, and l-theanine is a beneficial component.

The clinical trials on l-theanine show that there may be mild benefits for anxiety for some people. More interesting, and perhaps related to decreasing anxiety, are the benefits for reducing and modulating the immune response. Overall, theanine is generally regarded as safe and seems to have few safety concerns.

Genetic Lifehacks
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Curcumin Supplements: Decreasing Inflammation

Have you heard that curcumin supplements offer a slew of health benefits but are not sure why? Curcumin, a polyphenol found in turmeric, is a spice used in traditional Indian cuisine and in other areas of Asia as a drink. Turmeric is harvested from the rhizome of *Curcuma longa*, which is a member of the ginger family. It has a long history of use both as a spice and in traditional Ayurvedic medicine.

Curcumin is anti-inflammatory and decreases oxidative stress. It inhibits TNF-alpha and decreases NF-kB.

Benefits of curcumin:

Curcumin is a well-studied polyphenol, with randomized, placebo-controlled trials as well as tons of animal and cell studies.

The main effect of curcumin is a decrease in inflammation through a reduction in inflammatory cytokines. This decrease in inflammation impacts a variety of different chronic conditions such as arthritis, diabetes, NAFLD, and cognitive function.

Clinical trials using curcumin:

Hundreds of randomized, placebo-controlled clinical trials have investigated the efficacy of curcumin for a variety of different conditions. Here are just a few of the trials:

Diabetes prevention: A clinical trial that included 240 participants assessed the efficacy of curcumin for preventing diabetes. The participants all had prediabetes, and half of the group took a curcumin supplement (500 mg/3 times a day) After 9 months, almost 1/5 of the control group had diabetes but none of the curcumin group had progressed. The curcumin-treated group had a decrease in HOMA-IR.[ref]

Related article: Read about diabetes and blood glucose genes

COVID-19: A clinical trial with 80 participants tested nano-curcumin for the effect on cytokine production in COVID-19 patients. Nano-curcumin decreased IL-6 and IL-1B secretion, which may be important in severe cases of COVID-19.[ref]

Depression: A randomized clinical trial showed curcumin (500 mg/2x per day) to be more effective than placebo for improving depression.[ref]

Related article: Depression and Inflammation

Osteoarthritis: A curcumin-phosphatidylcholine complex (Meriva) was effective in decreasing inflammatory markers and in decreasing joint pain.[ref] Another clinical trial found that curcumin (500mg / 3x per day) was as effective as diclofenac for osteoarthritis – but with fewer side effects.[ref]

NAFLD: A clinical trial with 50 fatty liver disease patients found that 1500mg/day of curcumin significantly decreased liver fibrosis and inflammatory markers.[ref]

Related article: Fatty Liver Disease Genetic Risk Factor

PCOS: The trial included women with PCOS who were taking metformin. The addition of curcumin additionally decreased blood glucose levels as well as LDL cholesterol.[ref]

Related article: PCOS genes

Gulf War Illness: A clinical trial looked at the effect of curcumin and several other natural supplements on the symptoms of Gulf War Illness. Only curcumin significantly reduced symptoms of GWI.[ref]

Related article: Genetic risk factors for Gulf War Illness

Schizophrenia: As an adjunct to regular antipsychotic medication, the addition of nanocurcumin significantly improved psychiatric symptom scores.[ref]

Sarcopenia: Muscle mass decline is a serious problem in the elderly. Curcumin supplementation increased handgrip strength and weight lifting strength compared to placebo.[ref]

Cognitive Performance: Curcumin supplementation improved cognitive performance in middle-aged, overweight people.[ref]

Neuroinflammation: A trial of curcumin plus fish oil showed a significant reduction in IL-1β levels.[ref]

Muscle pain after exercise: In a clinical trial, curcumin supplementation reduced delayed-onset muscle pain after exercise.[ref]

Curcumin decreases chronic inflammation:

While the many human clinical trials show that curcumin is effective at reducing symptoms in chronic inflammatory conditions, cell and animal studies elucidate the mechanism of action:

IL-17 reduction: Curcumin reduces IL-17 production through the induction of IDO (tryptophan enzyme in the kynurenine pathway).[ref]

Inflammatory cytokines: A randomized clinical trial of curcumin (1g/day) in people with metabolic syndrome showed statistically significant reductions in TNF-α, IL-6, TGF-β, and MCP-1.[ref]

What are the side effects of curcumin?

Phase I clinical trials show that curcumin is safe at high doses of 12 g/day.[ref]

Anecdotally, curcumin at higher doses may give some people intestinal issues. Thus, keep an eye out for gastrointestinal side effects and cut back if needed.

Absorption and metabolism of curcumin:

Curcumin is not very bioavailable – poorly absorbed, rapidly metabolized, and quickly excreted.[ref]

Many studies point to the fact that it is quickly metabolized and that the parent curcumin compound doesn't stick around long in the bloodstream.

Of note, though, is that recent research shows that some of the anti-inflammatory effects of curcumin are due to the curcumin metabolites, rather than curcumin itself. Research showed that the inhibition of NF-κB is due to the metabolite rather than the parent compound.[ref][ref]

Helping curcumin stick around longer:

Piperine, a compound found in black pepper, is sometimes combined with curcumin. Piperine interferes with glucuronidation, which is a route of curcumin metabolism. By slowing down glucuronidation, curcumin can remain in the system longer.[ref]

One clinical trial showed that 20 mg of piperine increase serum concentrations of curcumin for 1-2 hours after ingestion. The bioavailability of 2g doses of curcumin increased by 2000% (in humans).[ref]

Related article: UGTs: Glucuronidation genes

Increasing absorption of curcumin:

In the intestines, curcumin must cross the intestinal barrier for absorption. The gut bacteria in the intestines actually metabolize some of the oral curcumin that you take.

Using a surfactant that decreases the intestinal mucosa is effective in animal studies for increasing curcumin absorption.[ref] But surfactants or emulsifiers can cause intestinal inflammation and are not a good idea on a daily basis.

Related article: Emulsifiers and IBD

Combining curcumin with a fat is one way to boost absorption. Many of the different supplemental curcumin options take advantage of this option.

Curcumin nanoparticles: Theracurmin, a formulation with colloidal nano-particles, has a 27-fold higher bioavailability than powdered curcumin.[ref]

Curcumin phospholipid complex: A formulation of lecithin with curcumin increased absorption by about 29-fold in human trials. The brand used was Meriva, which is available from Thorne.[ref]

CURCUGEN: A patent-pending formula of curcumin and turmeric essential oil shows increased absorption ability in randomized trials. The CURCUGEN formulation increased free curcumin serum concentration by 16-fold compared to a standard powdered curcumin extract. CURCUGEN contains 50% curcuminoids, and it was compared to a 95% curcuminoid extract. The study used doses of each product that were equivalent to 2g of curcuminoids, so approximately 4g of CURCUGEN vs 2g of the 95% curcuminoid extract.

Curcumin metabolites: Some companies are creating metabolite versions of curcumin, with the focus on tetrahydrocurcumin as an active metabolite.

Cost-benefit analysis: Are more expensive curcumin supplements worth it?

Keep in mind that curcumin powder is fairly inexpensive, and turmeric is fairly cheap. Thus, it may be less expensive to take more powdered curcumin (or curcumin with piperine) than the more expensive, patented formulations with better bioavailability. You'll need to do the math...

You should also consider that some of the benefits of curcumin are derived from its metabolites, as opposed to the free curcumin being studied in absorption studies.

Genes that interact with curcumin:

GSTP1: Curcumin induces the expression of GSTP1 (glutathione S-transferase P1).[ref] GSTP1 is part of the body's detoxification system, responsible for getting rid of certain toxicants through conjugation with glutathione. GSTP1 is important in cancer prevention through its elimination of carcinogens.[ref] For women, GSTP1 is important in the way estrogen is metabolized, and promoting better GSTP1 function may help to decrease the risk of breast cancer.[ref]

Related article: Estrogen metabolism

Some people have GSTP1 variants that cause the enzyme not to function as well as normal, and curcumin may help to increase expression.

Check your genetic data for **rs1695** (23andMe v4, v5; AncestryDNA):

- A/A: typical; possibly higher IL-6 in men who take vitamin E[ref]
- A/G: typical risk of breast cancer
- G/G: reduced function, increased risk of breast cancer[ref][ref], increased risk of prostate cancer[ref], increased risk of nasal polyps[ref]

TNF-alpha: Curcumin decreases TNF-alpha levels. TNF-alpha is an inflammatory cytokine, important in the cellular defense against pathogens. Too much TNF-alpha can cause chronic inflammation and the downstream effects resulting in chronic disease.

Some people have genetic variants that increase their cellular production of TNF-alpha.

Check your genetic data for **rs1800629** -308A/G (23andMe v4, v5; AncestryDNA):

- A/A: Higher TNF-alpha levels. **Increased risk of:** ulcerative colitis[ref], celiac disease[ref] (note – must have HLA type also), septic shock[ref], diabetic foot ulcers[ref], asthma[ref] , Hashimoto's thyroiditis[ref], skin infections[ref], periodontitis[ref], asthma[ref] in children, COPD[ref], stroke[ref], gum disease[ref], heart disease[ref]; nasal polyps[ref], **Lower risk of:** Malaria (half the risk)[ref], osteoporosis[ref], stroke[ref]
- A/G: somewhat higher TNF-alpha levels – see above
- G/G: typical, better response to high protein/low carb diet

p53 (tumor suppressor): The TP53 gene encodes a tumor suppressor, called p53, which is important in preventing cancer. Studies have shown that curcumin increases p53 in colon cancer patients.[ref][ref] It is being studied as an adjuvant to chemotherapy.[ref]

Nrf2 and Keap1: Studies show that curcumin decreases inflammation through modulating Nrf2. The Nrf2 pathway regulates the expression of antioxidants created in the cells and counteracts cellular oxidative stress. Keap1 is a protein that has been identified as a repressor of Nrf2 activation. Recent research shows that curcumin inhibits Keap1 expression, thus repressing the repressor of Nrf2.[ref]

Nrf2 levels are partly impacted by genetics:

Check your genetic data for **rs6721961** (23andMe v4):

- G/G: typical
- G/T: typical
- T/T: significantly diminished Nrf2 expression, increased risk of lung cancer[ref]

Epigenetics and curcumin:

Epigenetics is the changing of gene expression. These aren't inherited changes to your DNA, but rather the increases or decreases in gene expression.

One way that genes turn 'off or on' is through histone modification. Histones control how your DNA is packaged up so that a gene can't be translated into a protein. Modifying histones, therefore, allows a gene to 'express' or turn into its encoded protein.

Curcumin has been shown in studies to be a potent inhibitor of histone deacetylases. This means that curcumin inhibits the enzymes that control how histones package up DNA and prevent it from being read. In fact, curcumin seems to be more effective at inhibiting histone deacetylases than drugs, such as valproic acid or sodium butyrate, which are well known for this function. The key, though, is that this occurs at levels similar to pharmacological drugs only when curcumin concentrations are fairly high.[ref] (Higher than through regular supplement levels, if I'm understanding the research right).

Let me give you an example…

One way that curcumin may help as an adjunct in cancer treatments is through acting as a histone modifier to increase p53. The tumor suppressor p53 often 'turns off' in cancer cells, and studies show that curcumin is one molecule that may be able to turn it back on.[ref]

Conclusion:

Curcumin is a well-studied natural supplement that has been tested in a myriad of clinical trials. It offers anti-inflammatory properties that may help with chronic diseases. There are many options for curcumin supplements, and you may find that experimenting with several types is the best way to find out what works for you.

Natural Supplements & Your Genes

Want to learn more about how supplements interact with your genes?

Check out all of the the Supplement research guides on Genetic Lifehacks.

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