

**Allergies & Immunity Supplement Guide **

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**Introduction**

In times of good health, we’re barely aware that our immune system even exists. Yet at any given time, we’re battling an invading horde that is invisible to the naked eye and can evolve much faster than we can.

Fortunately, we have a dedicated defense system against these germs, and it’s on call 24/7, fighting several threats at a time while readying for the next. But even so, we can still get sick, and when this happens, we become aware of the war taking place inside us.

From the latest pandemic down to those bothersome colds and allergies that somehow surprise us every year, we must face occasional reminders of the thin line we constantly walk between health and illness. Unsurprisingly, that’s when we start wondering how we can help our immune system keep us healthy — or how we can reduce the duration and severity of an illness, should one strike.

Supplementation is a controversial topic, especially when its purpose is to avoid or mitigate illness. The field is full of scammers eager to exploit people’s fears for the purpose of making a quick buck. And even when we have the best intentions, we seldom have a good understanding of the science and are too eager to latch onto any potential cure. As we’ll see, though, the immune system is complex and multifaceted, making it tough to predict the effects that a promising supplement will have in real life.

As it stands, ravaging viral pandemics aren’t just a threat to overall health; they can also cause economies to come to a screeching halt. Our health is our greatest asset, but still, when money becomes scarce, we need to make especially sure it isn’t wasted on useless or even dangerous supplements.

Ironically (maybe), the main goal of this guide is to help you make good decisions about what not to take. As we’re about to learn, attempts to “boost” or “enhance” the immune system through supplementation with herbs or excessively large doses of a vitamin or mineral can end up doing more harm than good.

**Immunology 101**

From a historical standpoint, the field of immunology was launched when doctors observed that during periods of some pandemic diseases, individuals who became infected and didn’t die couldn’t be infected again; they were immune. Somehow, after the infection, the body was able to fight back, not only by killing off the initial infection but also by protecting against future infections of the same type. This, of course, would be the goal of any immune-boosting agent: to enhance this adaptive immune response. But there are two major parts to the immune system that work together, and the ability to fight off infections depends on their coordinated function.

**The innate immune system**

Think of the innate arm of the immune system as the first responder to insult, injury, or infection. It consists of multiple parts. Some epithelial cells, such as those in the skin, provide a physical barrier to pathogens that prevent their entry, and epithelial cells that line the airway also secrete antimicrobial substances. An array of specialized proteins are also present in our blood and are designed to bind to foreign invaders, tagging them for destruction by effector cells called macrophages or neutrophils, which rush in to gobble up bacteria or kill virus-infected cells.

The effector cells themselves express proteins called pattern recognition receptors (PRRs), which act as sensors for microbial infection. PRRs work by binding to specific molecules that are present on pathogens 3

and triggering the release of specialized proteins called cytokines. The type of cytokines released during an infection promote inflammation, which calls in additional immune cells to help.

One example of a PRR is toll-like receptor 4 (TLR4), which recognizes endotoxins (aka lipopolysaccharides, or LPS), which are molecules present on the cell walls of many bacteria. When present during a bacterial infection, LPS binds to TLR4 and stimulates the release of proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), and others, which send a “danger signal” that mobilizes the immune system to fight off the foreign invaders.

**The innate immune response to viral infection**

Some PRRs are also designed to detect viral infection by sensing DNA or RNA from viruses, which triggers antiviral responses. Let’s say you were exposed to a virus. As with other infectious agents, the innate immune system is again the first line of defense. Viruses make their entrance into host cells through specialized vesicles (membrane pouches) called endosomes. Within these endosomes are PRRs such as TLR7 or TLR8[1] that bind to and sense the presence of viral RNA, triggering the innate antiviral response. Should the virus escape from the endosomes and make it into the cytosol of the cell (i.e., the liquid inside of cells) — a likely event during an active viral infection — additional virus sensors, such as retinoic acid inducible gene I (RIG-I)[2] and others, detect the infection and sound the alarm.

The “alarm” consists of inflammatory cytokines and type I interferons (IFN), such as IFNα and IFNβ, that trigger the innate antiviral response. When initiated, the antiviral response deploys a number of countermeasures to slow the infection and induce an antiviral state in neighboring cells that haven’t been infected.[3] These measures brought on by the interferon response include cell death by apoptosis (programmed cell death), cell cycle arrest (to keep virus-infected cells from dividing), and mobilization of the adaptive immune system to fight the infection (more on that later).[4][5][6]

Although the innate antiviral system has evolved over thousands of years to help stop viral infections, the viruses aren’t helpless. They too have evolved a number of tricks to circumvent our antiviral defenses — by evading detection by the endosomal or cytosolic PRR sensors, for example.[7]

**Adaptive immune system**

Although the innate immune system is capable of stopping a virus on its own, some infections can’t be defeated by the innate response alone, particularly if that pesky virus has some tricks up its sleeve to evade detection. (The inability of the innate system to stop the virus is much more likely when we are sleep deprived, malnourished, or stressed). In these situations, the innate response continues to do its best to slow the rate of infection as much as possible while calling on the slower-acting (but much more targeted) adaptive immune system for help.

Adaptive immune system cells are called lymphocytes and include B cells and T cells. Unlike innate immune system cells, which recognize the general parts of microbes through PRRs, lymphocytes detect and deal with infections in a much more precise way. Each lymphocytic cell expresses a receptor unique to a certain type of pathogen. When it encounters the pathogen that it binds to, a lymphocyte produces a large amount of pathogen-specific effector cells. After massive cell cloning and then the elimination of the infection, some of the pathogen-specific cells stick around to provide long-term immunity.

In this way, the adaptive immune system has a type of memory. If you are exposed to the same infection down the road, you might not get sick (or as sick) because your body might rapidly recognize and fight off

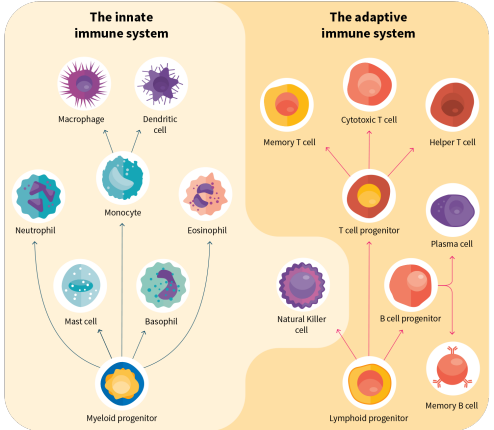
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microbes before the infection could ever take hold. In other words, you may be immune. For some pathogens — the measles virus[8]is a good example — immunity can last for years or even decades. For others, such as influenza, immunity is much shorter lived because the virus mutates and changes form yearly.[9]

**The innate and adaptive immune systems work together**

Although the innate immune system is the first line of defense and the adaptive system develops slower and is more targeted, this doesn’t mean that they function independently. Their activity is highly coordinated.

**Cells of the immune system**

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To visualize how this works, we can look at an overview of the process after the pathogen — a virus, for example — makes its way into the body. Let’s say you were unlucky enough to be exposed to a virus for which you have no immunity. It will likely enter through a mucosal surface (eyes, mouth, or throat) and infect the epithelial cells in the area. This will cause some cell death and an inflammatory response, which will change the endothelial lining of blood vessels in the area.

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Not only will the cells express different surface proteins, causing them to become “stickier”, but the spacing between cells will increase. This allows immune cells to adhere to the area and squeeze their way past the endothelial layer into the infected tissue. Specialized antigen presenting cells (APC) in the innate immune system, such as dendritic cells, gobble up cell debris and the virus at the infection site, grinding them up and presenting parts of them (i.e., antigens) on their cell surface on major histocompatibility complexes (MHC).

Loaded with antigen, the dendritic cells travel through the lymphatic system to a local lymph node, where they help trigger the adaptive immune response. (This is why the lymph nodes in your throat or elsewhere become swollen during an infection; APCs are accumulating to set off an adaptive immune response against the microbes expressing that particular antigen).

Once in the lymphoid tissue, the dendritic cell activates the naive T cells that happen to bind to that same antigen. The activated naive T cell then undergoes multiple rounds of cell division to increase in number and mature. There are three main types of effector T cells: cytotoxic T cells, helper T cells, and memory T cells.

Cytotoxic T cells (aka CD8 T cells) are the foot soldiers of the immune system.[10] After being activated in lymphoid tissue, they travel back to the infected area to attack and destroy infected cells.

Helper T cells come in a couple of varieties. TH1 cells travel back to the infected tissue, where they help activate innate immune cells such as macrophages. In contrast, TH2 cells remain in the lymphoid tissues, where they interact with antigen-specific B cells and induce them to produce antibodies.

B cells bind to antigens through their B cell receptor (BCR). When a B cell encounters an activated TH2 cell in the lymph node that also happens to bind to parts of the same pathogen, the B cell activates undergoing multiple rounds of cell division and mutation to select those cells with the best antibodies. Ultimately, they differentiate into the two main types of B effector cells: plasma cells and memory B cells.

Plasma cells are professional antibody producers and are purposely built to make and secrete large numbers of antibodies. These antibodies operate at the business end of adaptive immunity, binding to and neutralizing pathogens as well as flagging them for destruction by other immune cells.

Finally, after an active infection, a subset of antigen-specific B and T cells stop short of differentiating into effector cells and remain in a preactivated state, ready to spring into action at the slightest sign of infection. These memory cells give us long-term immunity, also called immunological memory.

Vaccines are a great example of immunological memory. They protect us by artificially introducing parts of a bacterium or virus. By injecting part of the microbe (or whole microbes that have been killed and are not capable of infection), the body generates an adaptive immune response against that pathogen. After immunological memory is established, if you were exposed to the live virus or bacteria in the future, you wouldn’t get sick (or as sick) because you’d have some immunity.

**Why immune boosters don’t make sense, even on paper**

As we’ve learned, the immune system is complex and multifaceted, consisting of an early-acting/always-on innate system and a potent-and-precise but slower-developing adaptive system. They work together, and much of the crosstalk between them is controlled by the release of inflammatory cytokines and inflammation. Given this, if we were to consider what boosting the immune system might look like and how

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we would accomplish it, all of a sudden immune boosters don’t look so promising.

**Supplements to target inflammation?**

There are certainly plenty of supplements for inflammation out there, and they work…to a point. But do we really want to suppress inflammation, when the timely release of proinflammatory cytokines during an initial infection is key to slowing the infection and activating the adaptive immune system? Probably not. And attempts to do so could be the difference between prolonged illness and good health — or even life and death with new pathogens that have jumped from animals to humans, such as SARS-CoV-2, the virus that causes COVID-19.

Increasing inflammation is also a nonstarter because too much is not a good thing at all in this case. Many deaths from respiratory viruses such as influenza or COVID-19 are caused by a so-called “cytokine storm”,[11] which is an overreaction of the immune system that creates massive amounts of inflammation that can lead to organ failure and death.

**What about antioxidants?**

Antioxidants are certainly important during an active infection, but immune cells also tend to attack pathogens via an oxidative mechanism.[12] Although there are some links between vitamin C intake and resistance to upper respiratory viruses — vitamin C is included as a primary option for this reason — it is important not to overdo it, which could interfere with the mechanism. But we are talking about immune boosters here, and antioxidants are not that.

**Do we really want to boost the immune system?**

There’s a fine line between immunity and autoimmunity, and the latter occurs when the adaptive immune system becomes overactivated and begins attacking our own cells, tissues, and proteins. A hallmark of adaptive immunity, when it is working properly, is that it turns off after the infection is defeated. If allowed to persist, immunity can be developed against our own cells and tissues. This happens in autoimmune conditions such as lupus,[13][14] rheumatoid arthritis,[14] and Sjogren’s syndrome,[15]in which the adaptive immune system is inappropriately keyed up on “self” proteins. There may be a fine line between autoimmunity and a “boosted” immune system.

**In summary**

To stay healthy and infection free, the innate and adaptive immune systems need to be robust enough to fight off invading microbes but regulated enough that they don’t do too much damage to our own cells, proteins, and tissues. We don’t accomplish this by taking buckets of supplements, clumsily targeting inflammation or any other signaling process. Instead, this is accomplished by taking care of ourselves.

That means being well nourished, sleeping enough, staying properly hydrated, and controlling stress to the extent possible. There are certain micronutrients and supplements that can support a high-functioning immune system, and we’ve included them in this guide. But without taking care of yourself, the supplements 7

amount to a drop of water in the ocean.



Bill Willis, senior researcher PhD in Biomedical Science

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**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. |
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**Core Combo**

If your blood levels of vitamin D (25(OH)D) are adequate or if you don’t know your levels, 400 IU (10 μg) of vitamin D3 per day may help maintain levels in the adequate range. A dose of 400–1000 IU is generally effective for reducing the risk of acute respiratory infections.

If your 25(OH)D levels are low, 800–2,000 IU (20–50 μg) of D3 per day is likely to raise them to an adequate level, at which point 800–1,000 IU (20–25 μg) per day should suffice for maintenance. In case of full-blown deficiency, consult your physician because a medically supervised intervention may be needed.

Because vitamin D is fat-soluble, it is better absorbed when taken with a fat-containing food or supplement (e.g., fish oil).

**Specialized Combos**

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**For people who easily get sick**

Consider your vitamin D levels as per the core combo.

Take 200–1,000 mg of vitamin C daily. For vitamin D, a dose of 1,000 mg is more commonly studied, though it’s possible that lower amounts are equally effective. Vitamin C can cause gastrointestinal adverse effects, so starting small and increasing the dose slowly may help to avoid discomfort.

Although its usefulness is questionable, 2,400 mg per day of echinacea extract taken in 3 divided doses may somewhat reduce the risk of getting a cold.

**At the onset of a sickness characterized by cold-like symptoms**

Take zinc acetate lozenges every 1.5 to 3 hours (75–95 mg of zinc per day). Ideally, start within 24 hours of experiencing the first symptoms of a cold — if you start later, the lozenges may still help, but they may be less effective.

**Stop after 2 weeks or as soon as the symptoms disappear, whichever comes first.** Over time, such high doses of zinc can irritate the gastrointestinal tract. They can also cause a copper deficiency because zinc kickstarts the process of creating metallothionein, a protein that binds zinc, but also other metals, notably copper. The bound metals then leave the body as waste products.[16][17] Even higher doses of zinc can

damage the liver and kidneys, so be careful not to cumulate zinc supplements (the lozenges mentioned in this guide and the zinc in a multivitamin, for instance).

Although more speculative, there is little downside to using honey as a cough syrup (besides calories). Taking 5 to 10 mL every 6 hours may help to alleviate cough symptoms.

Another speculative option is 4,000 mg per day of echinacea extract taken in 5 divided doses. **For people with seasonal allergies**

Consider your vitamin D levels as per the core combo.

In addition to the core supplements, take spirulina (2 grams/day). This is fairly speculative, but the guide doesn’t currently contain better options.

Another even more speculative option is 500 to 2,000 mg of Nigella sativa oil daily. Larger doses (>1,000 mg/day) should be taken evenly throughout the day.

**For older adults**

Consider your vitamin D levels as per the core combo.

If you are underconsuming vitamin E or have low blood levels of vitamin E, take 200 IU (134 mg of natural α-tocopherol or 90 mg of synthetic α-tocopherol) per day. Because vitamin E has anticoagulant properties, make sure that your diet contains at least your Adequate Intake (AI) of vitamin K (90 μg/day for women; 120 μg/day for men).

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**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 Allergies & Immunity 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:

Honey

Quercetin

Nigella sativa

Ginger

Probiotics

Fish oil

Changed ranking:

Garlic

Downgraded from primary to unproven. The previous version of the guide put far too much emphasis on mechanistic plausibility and too little emphasis on randomized trials. Although it is very plausible that garlic could reduce the risk of infections, we still need many more trials to be conducted.

Elderberries

Downgraded from promising to unproven. A new evidence review suggested that it was less effective than previously thought

N-Acetylcysteine

Downgraded from promising to unproven. New evidence standards mean that we’re not confident in the preliminary research supporting N-acetylcysteine. It may be effective and is mechanistically plausible, but we need to see more research.

Removed:

Pelargonium sidoides

The evidence review would have taken too long for the current update. We will add it back during the next small update to the guide.

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**Primary Supplements**

**Vitamin C (For mitigation of colds) What makes vitamin C a primary option**

Vitamin C is an essential water-soluble vitamin with antioxidant properties. The ability to protect against oxidative stress ultimately generated interest in the potential of supplemental vitamin C to improve immunity, in combination with data from a collection of animal studies demonstrating that vitamin C affects resistance to infection by viruses and bacteria.[18]

Most of the research in this area pertains to the effects of supplemental vitamin C on the common cold. During the 1970s, there was enormous public interest in this topic thanks to the work of Linus Pauling. Since then, the efficacy of vitamin C for improving other immunity-related outcomes — such as COVID-19, most recently — has been examined in a swath of studies.

Daily supplementation with vitamin C might reduce the risk of developing the common cold, to a trivial degree.[19] Slightly stronger evidence indicates that daily supplementation with vitamin C could reduce the severity and duration of the common cold in people who develop the illness, although the potential benefits appear to be modest.[19] Additionally, evidence from a few studies indicates that supplementing with vitamin C notably reduces the risk of developing the common cold in people who are undergoing heavy acute physical activity (e.g., marathon runners).[19]

If supplementing begins after common cold symptoms have already manifested (as opposed to regular daily supplementation indefinitely), vitamin C does not appear to affect the severity or duration of the common cold.[19]

There are a limited number of studies that have investigated whether supplemental vitamin C reduces the risk of developing pneumonia or enhances the efficacy of standard treatment for pneumonia. It’s currently unclear whether vitamin C has a beneficial effect on either of these outcomes,[20] and thus further studies are needed.

With respect to COVID-19, the collective body of evidence suggests that supplemental vitamin C reduces the risk of in-hospital mortality.[21][22][23] Supplemental vitamin C may also reduce COVID-19 severity.[22][23] Most of the studies examining the efficacy of supplemental vitamin C for reducing the risk of in-hospital mortality administered vitamin C intravenously, so further investigation is needed to determine whether oral supplementation can improve patient outcomes, especially in people without severe COVID-19, a population that has not been widely studied.

Although the magnitude of benefit isn’t remarkable, there is a healthy body of evidence investigating the effects of supplemental vitamin C on the common cold, which increases confidence that regular supplementation reduces the duration and severity of the common cold in people who develop it. It’s also probable that regular supplementation with vitamin C reduces the risk of developing the common cold, although the magnitude of benefit may not be of practical importance, with the exception of people who are undergoing heavy acute physical activity in whom the reported risk reduction is pronounced.

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In addition, although the research pertaining to the effects of vitamin C on COVID-19-related outcomes is in its infancy, the flurry of studies published so far provides sufficient evidence to indicate that intravenous vitamin C has a beneficial effect on mortality in people hospitalized due to COVID-19.

For these reasons, vitamin C is currently ranked as a primary option.

**Warnings about vitamin C**

Excessive vitamin C supplementation can cause diarrhea and nausea, among other gastrointestinal issues.

Do not exceed 2 grams of vitamin C per day. For adults, the Tolerable Upper Intake Level (UL) for vitamin C is 2 grams per 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:https://doi.org/10.17226/9810

**How to take vitamin C**

To reduce the risk of developing the common cold, studies have had participants — both those from the general population and those undergoing heavy acute physical activity — supplement with 200 to 1,000 milligrams of vitamin C daily.[19] The most common dosage studied for reducing common cold duration is

1,000 milligrams daily.[19] High doses may cause gastrointestinal issues, so starting small and increasing the dose slowly may lead to the least discomfort.

Studies have reported a reduced risk of COVID-19-related in-hospital mortality with lower (≤1,000 milligrams per day) and higher dosages (1,000–9,999 milligrams per day) but not very high dosages (>10,000 milligrams per day).[21] Again, most of the studies in this area administered vitamin C intravenously, so the results are not necessarily generalizable to oral supplementation.

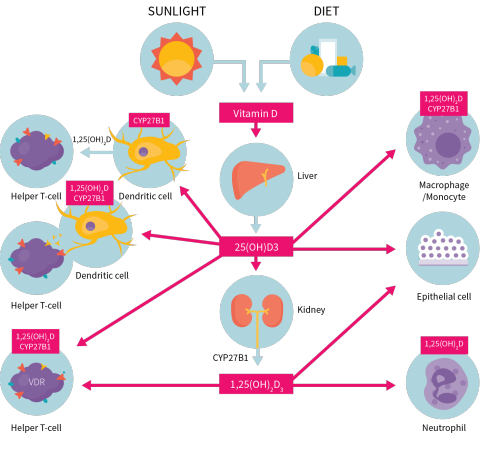
**Vitamin D (For prevention of acute respiratory infections)**

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**What makes vitamin D a primary option**

Vitamin D is an essential fat-soluble vitamin that is produced in the skin when it is exposed to sunlight and can be obtained through a variety of foods (e.g., oily fish) and fortified beverages. Vitamin D has a wide variety of roles in the body, including regulation of the immune system. There are vitamin D receptors on most immune cells, and consequently, vitamin D has the ability to modulate both the innate and adaptive branches of the immune response.[24] Vitamin D is also involved in the production of antimicrobial peptides and downregulates the production of proinflammatory cytokines while upregulating the production of anti inflammatory cytokines.[25]

**The immunomodulatory effects of vitamin D**

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In addition, evidence from a multitude of studies suggests an increased risk of acute respiratory infections (ARIs)[26] and allergies (e.g., asthma, eczema, food allergy)[27][28][29] with lower blood vitamin D (i.e., 25- hydroxyvitamin D) levels. For all these reasons, there is major interest in the use of supplemental vitamin D to improve allergy-related and immunity-related outcomes.

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Types of respiratory tract infections

| **UPPER RESPIRATORY TRACT INFECTIONS**  **(URTIs)** | **LOWER RESPIRATORY TRACT INFECTIONS**  **(LRTIs)** |
| --- | --- |
| Common cold | Bronchiolitis |
| Laryngitis | Bronchitis |
| Otitis media | Pneumonia |
| Pharyngitis and tonsillitis | Tracheitis |
| Rhinitis |  |
| Rhinosinusitis and sinusitis |  |

Collectively, the available evidence suggests that supplementation with vitamin D reduces the risk of developing one or more ARIs, to a small degree.[30][31]It’s likely that the magnitude of benefit has been underestimated in the primary analysis in these studies due to heterogeneity between the included studies because subgroup analyses indicate that the frequency, dose, and duration of vitamin D supplementation has a notable effect on the results (see “How to take” section for more information on the most effective dosage). Additionally, supplementation with vitamin D reduces the risk of influenza infection.[32]

However, although vitamin D appears to be useful for the prevention of ARIs, there is a lack of evidence to support its efficacy for the treatment of ARIs, namely, pulmonary tuberculosis and pneumonia.[33]

With respect to COVID-19, there is evidence to suggest that supplementation with vitamin D can reduce the risk of ICU admission in hospitalized patients.[34][35][36][37] Limited evidence suggests that supplemental vitamin D could also reduce the risk of requiring mechanical ventilation,[36][35] but further research is needed to confirm this. In contrast, supplemental vitamin D does not appear to affect the risk of in-hospital mortality,[36][35][37] nor does it seem to reduce the length of hospital stay.[35][36]

Moving on to allergy-related outcomes, supplementation with vitamin D has been found to reduce the risk of asthma exacerbation in children, but only in those with deficient blood vitamin D levels.[38] Supplementation with vitamin D has also been found to reduce eczema severity in children with blood vitamin D levels less than 30 ng/mL (but not in those with higher levels), as well as improve allergic rhinitis symptoms.[38]In contrast, maternal supplementation with vitamin D during pregnancy does not appear to affect the offspring’s risk of developing an allergy during childhood.[39]

In sum, there is a healthy body of evidence demonstrating that supplementation with vitamin D probably reduces the risk of developing one or more ARIs. Although the magnitude of benefit isn’t remarkable overall, it’s apparent that — with the right dosage — supplemental vitamin D may exert a practically meaningful reduction in ARI risk. Additionally, there is sufficient evidence to support the use of supplemental vitamin D for reducing the risk of infection by the influenza virus. For these reasons, vitamin D is currently ranked as a primary option.

**Warnings about vitamin D**

Vitamin D is a fat-soluble vitamin that can accumulate to toxic levels with prolonged excessive intake. Vitamin D toxicity, also called hypervitaminosis D, results in hypercalcemia and a host of symptoms including nausea, muscle weakness, loss of appetite, thirst, and excessive urination, to give an incomplete list. It can also lead to kidney stones, irregular heartbeat, and sometimes renal failure. The tolerable upper

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limits for vitamin D intake according to the NIH are listed below.

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

| **AGE/SITUATION** | **DOSE (IU)** |
| --- | --- |
| 0–6 months | 1,000 |
| 7–12 months | 1,500 |
| 4–8 years | 2,500 |
| 9–13 years | 3,000 |
| 14–18 years | 4,000 |
| >18 years | 4,000 |
| Pregnant and breastfeeding | 4,000 |

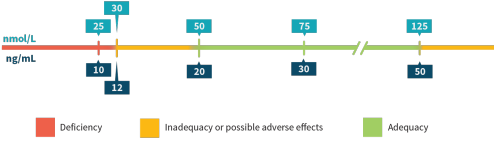
Exceeding these limits won’t necessarily lead to vitamin D toxicity, and higher doses have been shown to be safe in the short term, without increasing calcium levels to a harmful degree.[40] However, in the long term, especially without frequent vitamin D testing, it is unwise to exceed the amount of vitamin D needed for healthy bodily functions because it all ultimately comes down to vitamin D status, and people with already sufficient levels may be especially at risk of overdoing it.

There are some studies that suggest an increase in falls for older adult participants who are taking vitamin D supplements in doses greater than 1,000 IU per day.[41][42][43]It’s currently unclear why this happens or whether it might be mitigated by other fat-soluble vitamins such as K and A, so caution is warranted.

**How to take vitamin D**

First, determine whether supplemental vitamin D is necessary by checking current vitamin D levels — specifically blood levels of 25-hydroxyvitamin D (25(OH)D).

**Serum 25(OH)D concentrations**

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**Reference:** Institute of Medicine. Overview of Vitamin D (chapter 3 in Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press. 2011. DOI:10.17226/13050)

In case of deficiency, a medically supervised intervention may be needed. **Do not begin any intervention without discussing it with a physician.**

Studies that reported a reduced risk of ICU admission in participants with COVID-19 have used large doses of vitamin D3, given either in a single, high-dose bolus (e.g., 200,000 IU) or provided intermittently.[34] Most

commonly, the following dosage strategy has been used: a 21,280 IU bolus on day 1; a 10,640 IU bolus on 16

day 3 and another on day 7; followed by a 10,640 IU bolus given approximately once per week. As such, it’s unclear whether daily supplementation with a much lower dose (≤4,000 IU/day, i.e., the Tolerable Upper Intake level) would have similar effects, especially in people with COVID-19 who are not hospitalized, a population that has not been widely studied in this context.

For reducing the risk of developing an acute respiratory infection, the evidence indicates that the most effective dosage is to take 400 to 1,000 IU daily.[30]It’s currently unclear what the most effective dosage is for reducing the risk of influenza infection. In the meta-analysis that reported a protective effect, the dosage in the included studies ranged from 500 to 6,800 IU per day to 100,000 IU per month.[32]

It’s also unclear what the most effective dosage of vitamin D is to improve allergy-related outcomes in children. In the meta-analysis that reported improvements in allergic disease symptoms, most studies had the participants supplement daily with a dose of 500 to 4,000 IU.[38] However, some of the included studies had the participants take a bolus of vitamin D (14,000–60,000 IU) weekly or monthly or an even higher dose taken once during the study. According to subgroup analyses, the dosing strategy did not influence the effect of vitamin D.

Recommended Dietary Allowance (RDAs) for vitamin D (IU\*)

| **AGE** | **MALE** | **FEMALE** | **PREGNANT** | **LACTATING** |
| --- | --- | --- | --- | --- |
| 0–12 months | 400\*\* | 400\*\* | — | — |
| 1–13 years | 600 | 600 | — | — |
| 14–18 years | 600 | 600 | 600 | 600 |
| 19–50 years | 600 | 600 | 600 | 600 |
| 51–70 years | 600 | 600 | — | — |
| >70 years | 800 | 800 | — | — |

\* 40 IU = 1 μg | \*\* Adequate intake (AI)

**Reference:** Institute of Medicine. Dietary Reference Intakes for Adequacy: Calcium and Vitamin D (chapter 5 in Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press. 2011. DOI:10.17226/13050).

Because vitamin D is fat soluble, it is better absorbed when taken with a fat-containing food or supplement (e.g., fish oil).

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**Secondary Supplements**

**Zinc (For mitigation and prevention of colds)**

**What makes zinc a secondary option**

Zinc is an essential nutrient for the proper functioning of the immune system, and severe zinc deficiency increases the risk for infection.[44][45][46] Zinc lozenges can also limit virus replication in the nasal epithelium by preventing their binding to cells.[47] Zinc may also inhibit vital functions of viruses.[48][49]

The most common approach for using zinc to prevent and treat colds is to take a high-dose lozenge, and this approach may be particularly useful for maximizing its antiviral potential.

One meta-analysis of randomized trials on zinc for respiratory tract infections found that taking zinc lozenges after developing an infection can probably lead to a modest but meaningful reduction in the duration of symptoms for participants without zinc deficiency.[50] The risk of infections was lower in studies that used a zinc nasal spray supplying 1.2 mg daily, and in one study, a 45 mg dose of oral zinc, though not in the studies in which zinc was given as an adjuvant after administration of a rhinovirus. However, the risk for nonserious adverse events was increased in the case of both lozenges and nasal spray, and the evidence for benefits (besides for zinc lozenges) is weak, especially for any particular outcome when using any particular delivery method.

To summarize the implications, sufficient zinc status is important for immune function, though it’s unclear whether higher levels than deficiency will reduce general respiratory infections or reduce their severity. However, if zinc is administered in high doses in the form of sublingual lozenges during an infection, the influx of zinc will probably reduce the duration of the infection, with some side effects. This high dose is necessarily a short-term strategy because high doses in the long term will cause zinc toxicity, Additionally, it’s unclear whether zinc-containing nasal sprays can prevent infection, but the current evidence supports it, though with an increase in adverse events (and there are numerous other types of nasal sprays that may be superior).

Zinc for COVID-19

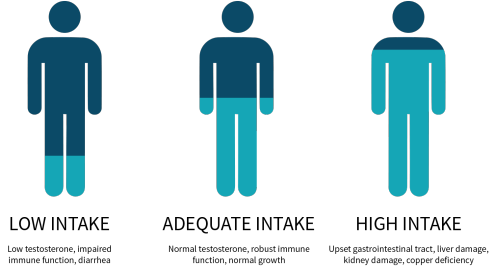
When it comes to COVID-19, although there have been studies, the evidence is still very preliminary, and it is difficult to come to any solid conclusions about zinc. For now, we must call it an unproven supplement for this purpose.

**Warnings about zinc**

Zinc is considered safe for adults in amounts less than 40 mg per day.[51] When this level of intake is exceeded, nausea, vomiting, stomach cramps, and even diarrhea can occur.[51]

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**Effects of low, adequate, and high zinc intake**

****At the same time, insufficient zinc intake can also cause gastrointestinal issues; it’s all about balance.

If too much zinc is taken — generally, more than 100 mg — for a long time, it can also decrease levels of copper, an important mineral needed for iron absorption and red blood cell formation.[16] Chronic zinc consumption or very high doses over a short period may also decrease the immune response[52] and reduce levels of HDL-C.[51]

Zinc can also interact with quinolone and tetracycline antibiotics, such as ciprofloxacin and doxycycline.[53][54] Taking zinc along with these antibiotics can reduce the amount of each that is absorbed. To reduce this effect, the antibiotic should be taken at least 2 hours before or 4 to 6 hours after zinc.[55][56] Other medicines, such as chlorthalidone and hydrochlorothiazide, can increase zinc in urine, so taking these thiazide diuretics could decrease the amount of zinc in the body.[57] Knowing what dietary supplements a person takes is important for doctors and pharmacists so they can check for any interactions.

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| **Caution: Zinc Tolerable Upper Intake**  (ULs) of Zinc in Milligrams  **AGE MALE OR FEMALE (including pregnant or lactating women)**  0–6 months 4  7–12 months 5  1–3 years 7  4–8 years 12  9–13 years 23  14–18 years 34  >18 years 40  Reference: Zinc[51] |
| --- |

**Zinc nasal sprays, swabs, and gels carry a risk of temporary or permanent loss of smell and possibly taste; they should be avoided.**

**How to take zinc**

Tor a cold, suck on zinc acetate lozenges every 1.5 to 3 hours (75–95 mg of zinc per day). Ideally, start within 24 hours of experiencing the first symptoms of a cold — if started later, the lozenges may still help, but they may be less effective.

**Stop after 2 weeks or as soon as the symptoms disappear, whichever comes first.** Over time, such high doses of zinc can irritate the gastrointestinal tract. They can also cause a copper deficiency because zinc kickstarts the process of creating metallothionein, a protein that binds zinc but also other metals, notably copper; the bound metals then leave the body as waste products.[16][17] Even higher doses of zinc can

damage the liver and kidneys, too, so be careful not to cumulate zinc supplements (the lozenges mentioned in this guide and the zinc in a multivitamin, for instance).

Experiencing headaches, nausea, vomiting, loss of appetite, stomach cramps, or diarrhea are signs that a person may be taking more zinc than the body can stand; if this happens, stop supplementing with zinc. (Of course, if these symptoms persist after supplementation is stopped, then the culprit is probably the cold, not the zinc.)

Because calcium, iron, magnesium, and zinc compete for absorption, it is better to take them at least 1 hour apart. Although to a lesser extent than magnesium, zinc may also impair the absorption of antibiotics, notably the tetracycline (e.g., doxycycline) and quinolone (e.g., ciprofloxacin) classes, so consider taking zinc and antibiotics at least 6 hours apart. Zinc can also impair the absorption of penicillamine, a drug used to treat rheumatoid arthritis, so these should be taken at least 2 hours apart. Thiazide diuretics may increase zinc excretion, thus causing zinc deficiency if taken in the long term.[58]

Zinc can lower blood sugar and may have additive effects when taken with other supplements or pharmaceuticals that can lower blood sugar, such as antidiabetic drugs.

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**Promising Supplements**

**Echinacea (For prevention of upper respiratory tract infections)**

**What makes echinacea a promising option**

Echinacea is a genus of flowering plants originating from North America and traditionally used in the medicine of indigenous Americans.[59]In particular, echinacea purpurea and angustifolia are the main species used for medicinal purposes, though others are sometimes used. Echinacea contains numerous phytochemicals (notably, alkylamides) that have roles in stimulating the immune system and aiding cell differentiation, function, and cytokine secretion in various immune cells.[59]

A meta-analysis of double-blind randomized trials on echinacea for upper respiratory tract infections found a reduction in the rate of infection based on 8 studies, all of which were largely in agreement.[60] There was some evidence for a reduction in duration of infection, but it wasn’t statistically significant. Overall, these effects were not large, but they were potentially meaningful if genuine. The risk of bias wasn’t particularly large or particularly small across all studies, and the already modest effects may be somewhat biased in favor of echinacea’s efficacy, and therefore, the effect may be untrustworthy. However, for reduction in infection risk, most studies were at a low risk of bias, and it’s entirely possible that this amount of bias wouldn’t negate the effect entirely.

However, the study that had the greatest weight, greatest effect size, and produced the only statistically significant result was confounded by other ingredients in the intervention group that weren’t present in the control group. When the researchers did a sensitivity analysis and removed that study, the results from meta-analysis were still statistically significant, but the already modest effect was even smaller. Omitting that study in particular is fair, and without it, the case for echinacea’s evidence is clearly weaker.

The authors abandoned their plan to do a subgroup analysis on the most effective forms of echinacea because there was likely insufficient evidence to be able to reliably tell the difference. Echinacea purpurea was by far the most common species of echinacea.

Echinacea may be worth taking to prevent upper respiratory tract infections, but it is unlikely to make a substantial difference on its own and is best thought of as a speculative adjunct to other interventions.

**Warnings about echinacea**

Echinacea can be safe, with few or no side effects, when used for short-term or long-term durations. Supplemental echinacea taken at a dosage of 800 mg two times per day has been studied and used safely for up to 6 months in adults.[61] A rare but serious side effect that is associated with echinacea is severe allergic reactions.[62] Allergic reactions to echinacea might be more severe in children; therefore, their doctor should be consulted before initiating supplementation with echinacea.[63]

Echinacea is considered immunomodulatory, meaning that it can affect the immune system by stimulating 21

or suppressing it; therefore, it may change the effectiveness of immunosuppressant medications taken for inflammatory disease.[61] People with allergies or asthma should avoid the use of echinacea because it has the potential to cause severe allergic reactions that may exacerbate symptoms of ongoing allergies or asthma.[62]

Echinacea dietary supplements have been shown to be contaminated with a low level of molds, which may pose a health risk to consumers.[64] Contamination issues can affect the supplement quality, safety, and how well it works in the body; therefore, it is important to use regulated supplements.

**How to take echinacea**

The largest study used 2,400 mg per day of an Echinacea purpurea extract taken in 3 divided doses before infection and 4,000 mg per day taken in 5 divided doses upon catching a cold. Although the effect wasn’t the largest, many of the other studies are less reliable, and so it may be wise to treat this dose as the most likely to have benefit.

More research is needed to determine the optimal dose.

**Honey (For reduction in upper**

**respiratory tract infection symptoms) What makes honey a promising supplement?**

Honey has general antimicrobial effects due to a complex array of chemicals, primarily its phenolic contents, which come from pollen collected by bees.[65]It can improve the proliferation of several immune cells, and a component of honey, methylglyoxal, interferes directly with the function of HIV.[66]

A meta-analysis of randomized trials found a modest reduction in cough symptoms due to upper respiratory tract infections when taking honey in addition to normal care, with some potential evidence for superiority to diphenhydramine.[67] But because the evidence isn’t strong and the effect is modest, it’s difficult to say that the true effect for the average person is going to be particularly meaningful. It might, but we don’t know that, and more research is needed.

Although many types of honey were used across all studies, it’s impossible to determine which are most effective.

**Warnings about honey**

Honey is safe to ingest and apply to the body for adults and children older than 1 year of age. Children under 1 year of age should not be given honey because it can contain Clostridium botulinum, which can cause botulism, a serious illness that causes difficulty breathing, muscle paralysis, and possibly death.[68]

Honey that comes from the nectar of rhododendrons (a type of plant) can be unsafe to ingest. This type of honey contains grayanotoxins, which are highly toxic. Adverse effects that have been reported after the

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ingestion of rhododendron honey or “mad honey” include nausea, vomiting, sweating, dizziness, and weakness. Heart complications, low blood pressure, high heart rate, and chest pain from heart block were also noted in people who consumed this type of honey.[69]

Honey should be used with caution if taking anticoagulant or antiplatelet medications.[70] These medications are used to prevent blood clotting in people at high risk for developing strokes or heart attacks. Honey interacts with these medications by slowing down blood clotting, which can have an additive effect of increased prevention of clotting. This causes the blood to be thinner and leads to an increased risk of bruising and bleeding. Therefore, people who are taking these medications should consult their doctor before starting supplementation with honey.

People with diabetes should use honey in moderation because honey contains sugar, and this might increase blood sugar levels. People with diabetes should monitor their blood sugar levels throughout the day if they are taking honey and consult their doctor.

Contamination of honey is quite common and is usually from the environment or beekeeping practices.[71] Therefore, it is important for consumers to evaluate the origin of the honey being used and confirm that the honey has been monitored for contamination, especially for use in children older than 1 year. Bacteria, mold, or yeast can be found in honey, usually from the bees, nectar, or pollen. Additionally, pesticides, herbicides, or antibiotics have been previously discovered in honey.[71] People who want to take honey as a supplement must verify that their source of honey is free of contaminants by purchasing from regulated and sterilized productions.

**How to take honey**

Treat honey as a cough syrup and take 5 to 10 mL once every 6 hours, or longer if symptom relief persists. Honey can be combined with cough syrups and other interventions. Note that this amount of honey contains a meaningful amount of sugar and calories and may not be compatible with a given diet.

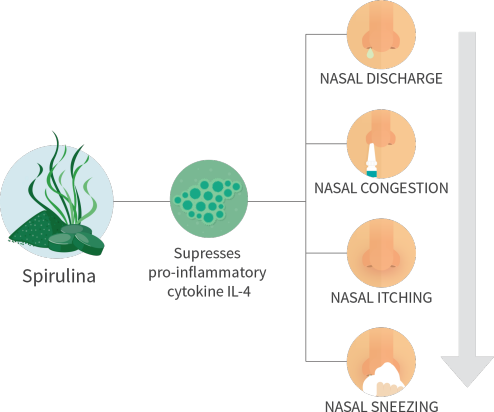
**Spirulina (for reduction of allergy symptoms)**

**What makes spirulina a promising option**

Spirulina is a blue-green algae and a member of the phylum cyanobacteria. It is of interest for improving allergies and immunity due to its robust antioxidant and anti-inflammatory properties,[72] which are primarily derived from its content of C-phycocyanin.[73] Supplementing with spirulina has been shown to modulate the secretion of cytokines, including interleukin 1-beta and interleukin 4.[74][75]

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**Effects of spirulina on nasal allergies**

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There is a lack of high-quality evidence from clinical trials in humans to indicate that supplementing with spirulina has beneficial effects on markers of immune function at large. In people with human immunodeficiency virus, there is weak evidence indicating that spirulina may increase the number of CD4+ T-cells and reduce viral load,[76][77][78] but these studies are limited by the lack of a placebo comparison and/or a small sample size. Moreover, conflicting findings are available.[79]

Spirulina has been shown to improve allergic rhinitis symptoms, namely, nasal itching, rhinorrhoea (runny nose), nasal obstruction, and sneezing.[80] Furthermore, it’s been demonstrated to be more effective than antihistamine medication for some of these symptoms.[75]

Spirulina is ranked as a borderline promising option for allergic rhinitis and for possibly improving immunity in people with human immunodeficiency virus. The main limitation at present is the small number of studies available. Further randomized controlled trials are needed in both of these areas to strengthen confidence in the efficacy of spirulina.

**Warnings about spirulina**

Spirulina supplements can become contaminated with toxic microcystins and β-methylamino-L-alanine (BMAA) from other types of cyanobacteria and microorganisms.[81][82] Early testing in 1998 and 1999 discovered potentially worrisome levels of microcystins.[83] However, the supplement industry seems to

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have largely cleaned up the production process, and in 2017, a report found that only 3 out of 14 products had meaningful levels of microcystins. Additionally, other reports from the U.S., German, and Italian markets didn’t find detectable levels of microcystins.[84][85][86] Similar information isn’t available for BMAA contamination, but the same methods used to reduce other cyanobacteria and microorganisms in spirulina will likely also help to reduce BMAA contamination.

Mercury, platinum, lead, and arsenic levels in spirulina products don’t appear to be excessively high, though it is possible that some products could be dangerous.[87][88] Needless to say, it’s always wise to purchase supplements from brands that do rigorous third-party testing to ensure safe products.

Spirulina has been found to reduce the activity of CYP1A2, CYP2E1 and CYP2C6, enzymes that are responsible for metabolizing a variety of drugs and whose inhibition may lead to overdose-like effects. Some of the relevant drugs can be found here, but people who take medications should talk to a doctor or a pharmacist.

**How to take spirulina**

For improving allergic rhinitis symptoms, studies have used a dosage of 2 grams of spirulina per day.

**Vitamin E (for improving general immune cell markers)**

**What makes vitamin E a promising option**

As a person ages, their immune system weakens against invaders and stressors. Supplementation with vitamin E can improve markers of immune function, but this does not necessarily translate into a reduced risk of catching infectious diseases. The evidence in this area is very mixed.[89][90]

Still, although more research is needed to better understand the effects of vitamin E on infection rates and illness severity, the current evidence suggests that older adults can benefit from vitamin E supplementation.

**Warnings about vitamin E**

Vitamin E has both antiplatelet and anticoagulant properties — the latter because it interferes with the blood-clotting properties of vitamin K.[91] This could be a problem for people whose diet is poor in vitamin K or who take blood thinners, such as antiplatelet agents (like aspirin) or anticoagulants (like warfarin/Coumadin and acenocoumarol/Sintrom).

Moreover, because of these antiplatelet and anticoagulant properties, 200 IU of vitamin E (the dose recommended for daily supplementation) may lower systolic blood pressure.[92] Note that supplements and pharmaceuticals that lower blood pressure can have cumulative effects.

Orlistat (Alli, Xenical) reduces how much fat is absorbed from food that is eaten. As a result, it also reduces the absorption of fat-soluble vitamins. People who take this medicine should take their vitamin E

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supplement at least 2 hours before or after.

**How to take vitamin E**

A person who intends to supplement with vitamin E should first track all foods eaten for a week; if they are getting less than 80% of the Recommended Dietary Allowance, on average, then supplementation becomes an option, though first they should try eating more foods rich in vitamin E.

Alternatively, a person could get their blood levels of vitamin E checked. Blood levels of alpha-tocopherol (α-tocopherol) that are less than 0.5 mg/dL (<5 μg/mL or <11.5 μmol/L) are considered deficient.

Recommended Dietary Allowance (RDA) for vitamin E (alpha-tocopherol) (mg/IU)

| **AGE** | **MALE** | **FEMALE** | **PREGNANT** | **LACTATING** |
| --- | --- | --- | --- | --- |
| 0–12 months | 4/6\* | 4/6\* | — | — |
| 7–12 months | 5/7.5\* | 5/7.5\* | — | — |
| 1–3 years | 6/9 | 6/9 | — | — |
| 4–8 years | 7/10.4 | 7/10.4 | — | — |
| 9–13 years | 11/16.4 | 11/16.4 | — | — |
| >13 years | 15/22.4 | 15/22.4 | 15/22.4 | 19/28.4 |

\* Adequate Intake (AI)

**Reference:** Institute of Medicine. Vitamin E (chapter 6 in Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. The National Academies Press. 2000. DOI:https://doi.org/10.17226/9810

Take 200 IU of vitamin E (134 mg of natural α-tocopherol or 90 mg of synthetic α-tocopherol).[93] Do not take more than 400 IU per day, and because vitamin E has anticoagulant properties, make sure that the diet contains at least the Adequate Intake (AI) of vitamin K (90 μg/day for women; 120 μg/day for men).

Because vitamin E is fat soluble, it is better absorbed when taken with a fat-containing food or supplement (e.g., fish oil).

**Quercetin# (For reduction of COVID-19 symptoms)**

**What makes quercetin a promising option**

Quercetin is a dietary flavonol found in a variety of plant foods such as vegetables, fruits, and nuts. It possesses immunoregulatory and cytoprotective properties, which can help curtail the inflammatory response and may help to reduce allergy symptoms and limit the damage that infections such as COVID-19 and influenza do to the body.[94]

Quercetin has been used in clinical settings during the COVID-19 pandemic, and a meta-analysis of 6 studies found preliminary evidence of meaningful benefits on the incidence of hospitalization and incidence of progression to intensive care, although the results for all-cause mortality didn’t reach statistical

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significance.[95] While encouraging, most of the research wasn’t at a low risk of bias, though given the impressive reduction in disease severity, it is probably fair to say that quercetin is more likely to help than not. These results may be largely due to quercetin’s antioxidant and anti-inflammatory effects that aid in reducing the damage to the lungs, and so extrapolation to general immunity is unwarranted.

One trial didn’t find general benefits during upper respiratory tract infections, although a subgroup analysis of older participants suggested a benefit in that context.[96] Another trial found a potential improvement in allergic symptoms due to pollinosis.[97] However, the evidence in these two conditions is highly preliminary

and speculative. Quercetin may confer benefits in the case of COVID-19, but more research is needed before we can have confidence in this.

**Warnings about quercetin**

Quercetin can safely be taken orally at daily doses of up to 1 gram for up to 12 weeks. The occurrence of adverse events is very low and mild. Headache and mild tingling has been observed after ingestion of up to 1 gram of quercetin per day for 4 weeks. Quercetin should be taken with caution when administered at doses greater than 1 gram for more than 12 weeks because this combination of dose and duration has not been studied in humans. Animal data suggest that people with estrogen-dependent cancer and kidney dysfunction should avoid high doses of quercetin because it promoted tumors and increased adverse effects in the kidneys.[98]

Quercetin can interact with cyclosporine, pravastatin, and fexofenadine; therefore, people who are taking these medications should use quercetin with caution. In human studies, an increased bioavailability of these medications was observed in participants who took quercetin, which means that the drug is absorbed and used by the body more quickly. The molecular mechanisms that can lead to increased drug bioavailability because of quercetin include inhibition of P-glycoproteins or inhibition of CYP3A4 enzymes in the intestines. People who are taking medications should consult with their doctor before initiating supplementation with quercetin.[98]

People with kidney disease should avoid high doses of quercetin because it can increase side effects related to kidney function or cause nephrotoxicity, based on studies conducted in rodents. Additionally, people diagnosed with estrogen-dependent cancer should avoid high doses of quercetin because it can increase tumor production.[98]

**How to take quercetin**

Upon the realization that one has COVID-19, taking 500 mg of quercetin per day split into 2 doses may confer a benefit. However, nowhere near enough research has been conducted to identify an optimal dose or be particularly confident in this one.

**Nigella sativa (For reduction of allergies and allergic asthma)**

**What makes Nigella sativa a promising option** 27

Nigella sativa, also known as “black cumin” or simply “black seed”, has been used for medicinal purposes in many parts of the world for centuries. Researchers believe that the primary active compound responsible for both the general anti-inflammatory and potent immunoregulatory effects is thymoquinone (TQ).[99][100] However, it is not only possible but rather likely that other phytoconstituents of the seeds and their amber colored oil, such as nigellidine or α-hederin, contribute to the cytokine-mediated reprogramming of immune cells behind the immunoregulatory effects of black seed, as well.[101][102]

What is particularly interesting about N. sativa is that it is an immune “modulator” in the truest sense of the word. It doesn't simply act as an immune booster or suppressor; rather, it appears to be as capable of ramping up the body's natural immune defenses against actual threats to health — such as pathogenic bacteria, viruses, fungal and parasitic infections, and even cancer — as it is of suppressing existing immune overreactions that are characteristic of many (auto)immune diseases.

Prior to the COVID-19 pandemic, research into the immunomodulatory effects of N. sativa was largely focused on allergies, mostly with promising results.[103][104] One study that stands out — and is therefore be discussed in detail here — tested the effects of topical intranasal application of N. sativa oil in the form of nasal drops in 68 participants with allergic rhinitis.[105]In their paper, the researchers report that the participants who applied 2 drops of black seed oil to their nasal mucosa 3 times a day for 6 weeks were approximately 3 times more likely to be symptom free at the end of the study period than their counterparts who received placebo drops containing only regular food oil (92.1% vs. 30.1%; p=0.000). Unfortunately, the researchers did not specify the exact amount of N. sativa oil per drop. However, it is reasonable to assume that the participants used a standard dropper, which suggests that each of the 3 daily applications delivered 2 doses of 0.05 to 0.10 mL directly to their nasal mucosa.

The positive results of the nasal drop study are not an application-dependent outlier. They are supported by at least 6 studies in which black seed was administered orally, and the researchers observed similar significant improvements in allergy symptoms in response to oral preparations of N. sativa in the form of oil and seed powder at daily doses ranging from 500 mg to 2,000 mg.[103][104]

With respect to a similar but different outcome, namely, allergic asthma, a recent meta-analysis reported significantly increased scores on the Asthma Control Test (ACT),[106] a questionnaire with items such as shortness of breath, night waking, interference with activity, use of rescue medication, and assessment of asthma control.[107] The meta-analysis included 4 randomized controlled trials (RCTs), but the ACT results are based on only 2 of them, in which 40 adults and 14 children received N. sativa oil in capsule form at daily doses of 1,000 mg and 15–30 milligrams per kilogram of body weight (mg/kg) for 4 and 8 weeks, respectively. Thus, although the current research supports the use of black seed as an antiasthmatic agent, the existing evidence must be considered preliminary, simply due to the small number of studies.

The number of studies conducted on COVID-19 during the pandemic was small, and many of them were limited by low participant numbers or methodological shortcomings such as lack of randomization or lack of a control, let alone a placebo group. A 2023 meta-analysis included only 3 RCTs in the final analysis.[108] What all 3 RCTs had in common was the researchers' hope of boosting their participants’ natural immune response to the virus without increasing the already high risk of the immune system going into potentially lethal overdrive,[101] and the extent to which the odds of dying from COVID may have been even greater than they had hoped. With an odds ratio of OR = 0.22, of the 1,113 COVID19-infected participants studied in the 3 trials, those who received a daily dose of 40 to 80 mg/kg of N. sativa seeds or two 500 mg capsules of N. sativa oil for 1–2 weeks were about 5 times less likely to die from their infection than their counterparts in the untreated arms of the studies.

Encouraging results were also seen in studies with less existential outcomes. These included a significant improvement in COVID-19 symptoms (cough, diarrhea, and fatigue) during the first week and increased 28

odds of a negative PCR test at 7 and 14 days in participants with mild-to-moderate COVID-19 infection in response to 900 mg per day of N. sativa oil and a 13% reduction in the time it took participants with mild COVID-19 to become symptom-free (10.7 ± 3.2 days vs. 12.3 ± 2.8 days in the control group) after taking only 500 mg of seed oil per day.[109][109]

Although the primary active constituents of black seed have well established effects on immune cells in the preclinical setting, practical research exploring the real-world benefits of thymoquinones, thymol, carvacrol, nigellidine, or α-hederin in the form of N. sativa supplements is still in the early stages. Therefore, and due to the limited number of studies and their significant methodological heterogeneity, scientific rigor, and overall quality, Nigella sativa must be considered a “promising” supplement for the treatment of (seasonal) allergies and acute viral infections.

**Warnings about Nigella sativa**

Nigella sativa is considered safe to consume and was well tolerated in adults who took 200 mg daily for 90 days.[110] A number of studies have confirmed the safe use of oral Nigella sativa, which seems to be well tolerated. The most common side effects seen with Nigella sativa supplementation are nausea, bloating, and a burning sensation in the stomach.[111]

Nigella sativa has been shown to inhibit the CYP3A4, 2C9, 2C11, 2C19, and 2D6 enzymes.[112][111]. This means that it could decrease the rate at which numerous drugs are metabolized by the liver and may lead to toxicity or overdose effects. Some drugs or supplements that are affected by these enzymes include quercetin, anticoagulants, antidepressants, and heart medication. The most common interaction between Nigella sativa and medications involves blood-pressure-lowering agents.[111]If a person is taking medications, it is important to consult a doctor before starting Nigella sativa.

Because Nigella sativa can lower blood pressure, taking it with other blood-pressure-lowering agents might lower blood pressure too much. People who are taking these medications should monitor their blood pressure closely and consult a doctor before starting Nigella sativa supplementation. Another interaction involves diabetes medications. Nigella sativa can lower blood sugar levels in the body, and taking Nigella sativa with other diabetes medications can cause blood sugar levels to drop too low. This can cause dangerous complications, like hypoglycemia, and therefore, blood sugar should be monitored throughout the day.

**How to take Nigella sativa**

Take 500 to 2,000 mg of N. sativa oil daily.

Larger doses (>1000 mg/day) should be taken evenly throughout the day.

N. sativa oil in bottles should be stored in a dark, cool place and consumed within 3 months of opening the bottle.[112]

Whole black seeds and powder at a daily dose of at least 2,000 mg offer an alternative to the more commonly used oil supplements. However, it should be noted that the pertinent studies with these sources report somewhat less consistent positive results compared to those using N. sativa oil.

An alternative third approach worth considering is the intranasal administration of black seed oil, which appears to be highly effective in alleviating the symptoms of allergic rhinitis. Although comprehensive comparisons of different dosing regimens are currently lacking, it seems reasonable to adopt the dosing 29

regimen used in the aforementioned study.[105] This consists of administering 2 drops (0.05–0.1 mL) of black seed oil per nostril 3 times daily.

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**Unproven Supplements**

**Elderberries**

**What makes elderberries an unproven supplement**

As with many plants, elderberry contains phytochemicals that can positively affect the ability of the immune system to function.[113] However, although a plant contains beneficial chemicals, that doesn’t necessarily mean that it will have meaningful effects in normal human contexts.

For human evidence, a meta-analysis evaluated a small number of studies that used elderberry supplements to prevent and treat colds and influenza. It found an overall lack of evidence for anything in particular, though what little research there is suggested a possible reduction in the duration and severity of colds, a reduction in the duration of influenza by some measures but not others, and a possible reduction in influenza severity, though the difference wasn’t statistically significant. Additionally, a randomized trial published afterwards failed to find clear evidence of a benefit in the context of people hospitalized for influenza.[114]

Therefore, the evidence is too weak to have confidence in elderberries for colds or influenza.

| **Digging Deeper: Elderberry and cytokine storms**  Some people on the web have warned that elderberry could initiate or exacerbate a cytokine storm, based on a study that showed increased cytokine production from elderberry intake.[115] The authors said that “in addition to its antiviral properties, Sambucol Elderberry Extract and its formulations activate the healthy immune system by increasing inflammatory cytokine production” (because cytokines are a natural and critical part of the immune system’s response to pathogens).  However, a cytokine storm isn’t a mere bump in cytokine production but is a severe immune overreaction to a pathogen. In cases of severe flu, cytokine storms are associated with outcomes ranging from lung inflammation to death.[116]  Although it appears unlikely that a low-to-moderate dose of elderberry would initiate a cytokine storm, nobody knows whether taking elderberry (especially in large amounts) when symptoms are severe has any adverse effects. Discuss supplementation thoroughly with a physician before using it. |
| --- |

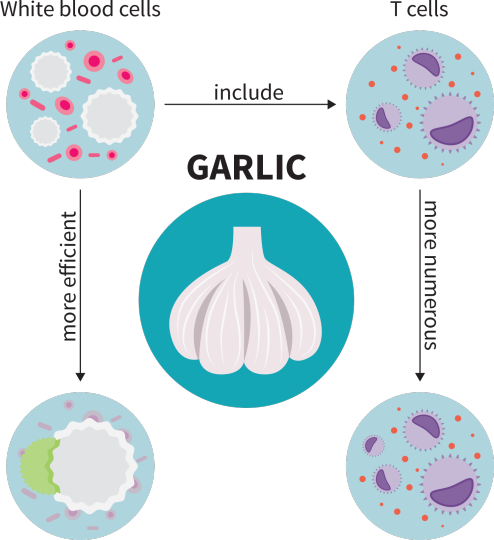
**Garlic**

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**What makes garlic an unproven supplement**

Garlic has broad effects on a number of immune cells, which improves their ability to fight invaders, and so it is mechanistically plausible that it could reduce the risk of colds and other infections.[117]

**Effects of garlic on white blood cells**

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Although the mechanistic rationale is high and there is much anecdotal evidence for garlic, the actual evidence for the prevention and treatment of infectious diseases is shockingly scant. Two trials have found potential effects on cold and flu,[118][119] and 1 has found a lack of effect in participants with COVID-19. For this reason, the evidence is insufficient, and much more research is needed.

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**Ginger**

**What makes ginger an unproven supplement**

Ginger contains potent anti-inflammatory chemicals, including gingerol and shogaol, which could potentially help curtail the allergic immune response. For this reason, it has also been hypothesized that ginger could be helpful in the case of COVID-19, which involves a large inflammatory response that damages the body.[120][121][122]

Unfortunately, there is scarce evidence for benefits, although what we currently have is encouraging. One trial found effects comparable to those of the drug Loratadine in the treatment of allergic rhinitis, and 1 found an a potential additional benefit of adding ginger extract to green tea, compared with green tea alone, in participants with cedar pollen allergies.[123][124] However, these trials are very preliminary, and we can’t be confident in the findings.

Similarly, although the 2 trials on COVID-19 are promising, we need more research before we can have confidence in ginger’s efficacy.[125][126]

**Probiotics/Synbiotics**

**What makes probiotics/synbiotics an unproven option**

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[127] After ingestion, these bacteria reside in the intestine and alter the overall bacteria population.

Synbiotics generally refer to products that contain both a probiotic and prebiotic (i.e., a substrate selectively utilized by gut bacteria, typically fermentable fibers). However, each component within a synbiotic does not have to fit the strict definition of either a probiotic or a prebiotic. Ultimately, whether a product is classified as a synbiotic comes down to whether the mixture of live microorganisms and substrates it contains confers a health benefit to the host.[128]

The interest in probiotics/synbiotics for improving allergies and immunity lies in the fact that stable, healthy gut microbiota are pivotal for overall health because the gut microbiota interacts with virtually all human cells. Moreover, the intestine contains the largest number of immune cells of any tissue in the body.[129]

Increasing evidence suggests that there is extensive cross-talk between the gut microbiota and the lungs and immune system, with the potential of the immune system and lung microbiota to affect the gut microbiota composition and the gut microbiota composition to affect the function of the immune system and lungs.[130][131] As a consequence of these interconnections, probiotics/synbiotics are thought to improve allergies and immunity by modulating the composition and/or function of the gut microbiota, resulting in benefits such as improvements in the immune response and inflammation.

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Before diving into research pertaining to which allergy-related and immunity-related outcomes probiotics/synbiotics may improve, it’s worth highlighting that the vast majority of evidence pertains to probiotic supplements, and few studies have examined the efficacy of synbiotics.

Additionally, it’s vital to note that many of the potential benefits of probiotics are strain specific.[132][133] Probiotics are identified by their specific strain, which also includes the genus, the species, and subspecies (e.g., Bifidobacterium animalis subspecies lactis DN-173 010). What this means is that the effects of one probiotic supplement are not generalizable to all probiotic supplements. For instance, two probiotic strains belonging to the same genus (e.g., Lactobacillus) and even the same species (e.g., Lactobacillus reuteri) can have different, strain-specific effects.

This concept of strain-specific effects is important when interpreting the research on probiotics because meta-analyses commonly pool data from studies using different probiotic strains, and it’s quite often the case that within a meta-analysis of 10+ studies, each study examined the efficacy of a different probiotic strain.

If such an analysis were to report a beneficial effect of supplementation with probiotics, what exactly can the reader take away? Again, it would be incorrect to conclude that probiotics in general elicit this beneficial effect because many of their effects are strain specific. Furthermore, it’s not possible to discern which specific probiotic elicited this beneficial effect because data were pooled from a multitude of studies that examined different probiotic strains. Finally, even if a person were to dig into the individual studies included in the analysis and locate which ones reported a beneficial effect in order to decipher which strains were efficacious — one study is insufficient evidence to support the efficacy of an intervention. For these reasons, caution is warranted in interpreting the evidence around probiotics for improving health outcomes.

To provide a concrete example of this possibility while also (finally) diving into the research on an outcome of interest, evidence from recently published meta-analyses indicates that supplementing with probiotics can alleviate allergic rhinitis (seasonal allergies and hay fever) symptoms.[134][135] However, none of these studies conducted strain-specific analyses.

Now, consider the results of another systematic review and meta-analysis published in 2022.[136] The qualitative portion of this study reported that probiotics improved at least one symptom of allergic rhinitis in 9 of 12 randomized controlled trials. Similar to the aforementioned studies, this suggests that probiotics are probably a good option for improving allergic rhinitis symptoms. However, there were only 2 probiotic strains evaluated in more than one study (each was evaluated in 2 studies). When the data were pooled for each strain, neither Lactobacillus paracasei LP-33 nor Lactobacillus rhamnosus GG was found to improve nasal symptom scores, the primary outcome of the meta-analysis. Therefore, it can be concluded that there is insufficient evidence to support the use of any specific probiotic for improving allergic rhinitis symptoms.

With this framework in mind for how to interpret the research pertaining to probiotics/synbiotics, let’s move on to the evidence concerning other allergy-related and immunity-related outcomes.

**Common infectious diseases**

A 2022 Cochrane review reported that supplementing with probiotics reduced the risk of developing an acute respiratory tract infection (ARTI) and reduced the duration of illness in people who developed an ARTI.[137] However, subgroup analyses were not conducted according to probiotic strain. In a separate review with more granular analyses, there was sufficient evidence to examine the efficacy of the species Lactobacillus casei and Bifidobacterum animalis subspecies lactis, neither of which reduced the risk of developing an ARTI.[138] However, there was evidence suggesting that Lactobacillus casei (but not Bifidobacterum animalis subspecies lactis) could reduce the duration of illness in those who developed an 34

ARTI. There is also limited evidence suggesting that synbiotics decrease the risk of developing an ARTI,[139] but it’s unclear how the composition of the synbiotic influences this effect.

Relatedly, evidence from a few studies indicates that the consumption of a fermented dairy product containing Lacticaseibacillus paracasei subspecies paracasei CNCM I-1518 or Lactobacillus casei DN-114 001 (along with the standard yogurt cultures Lactobacillus bulgaricus and Streptococcus thermophilus) might reduce the risk of developing one or more common infectious diseases (i.e., ARTIs and gastrointestinal tract infections), particularly acute upper respiratory tract infections.[140]

According to the results of one meta-analysis, probiotics may reduce the risk of developing at least one gastrointestinal tract infection (namely, diarrhea).[141] However, there were too few studies available for each type of probiotic to conduct subgroup analyses according to probiotic strain. A separate meta-analysis that examined the effects of probiotics in children and infants also reported that supplementation with probiotics reduced the risk of developing at one gastrointestinal tract infection,[142] and unlike the former, subgroup analyses were conducted.

The results from 2 trials each indicated that (i) supplementing with Lacticaseibacillus paracasei CBA L74 reduced the risk of developing at least one gastrointestinal tract infection by 51%; (ii) supplementing with Lacticaseibacillus rhamnosus GG reduced the number of days absent from childcare due to infection; (iii) supplementing with Limosilactobacillus reuteri slightly reduced the duration of a gastrointestinal tract infection; and (iv) supplementing with Bifidobacterium animal subspecies lactis BB-12 did not affect the incidence of gastrointestinal tract infection.

**HIV**

The results from 2 meta-analyses indicate that probiotics do not affect CD4+ T-cell count in people with human immunodeficiency virus (HIV),[143][144] although they may reduce the risk of disease-associated diarrhea.[144] However, neither study conducted subgroup analyses according to probiotic strain, so it remains to be determined whether certain strains can increase CD4+ T-cell count or are particularly effective for reducing the risk of disease-associated diarrhea. In a meta-analysis that only considered children and adolescents, there was evidence to suggest that probiotics can increase CD4+ T-cell count, but a different probiotic strain was used in each of the 3 studies included in the analysis.[145]

**Critical illness**

There is mixed evidence as to whether probiotics affect the risk of infections acquired in the intensive care unit (ICU).[146][147] There is also mixed evidence as to whether probiotics reduce the risk of ventilator associated pneumonia in this population.[146][148][149]

Among the meta-analyses cited above, only 1 study conducted subgroup analyses according to probiotic strain.[146] Neither Lactobacillus rhamnosus GG nor Lactobacillus casei affected the risk of ventilator associated pneumonia. It was reported that VSL#3 (a specific mixture of 8 probiotic strains) reduced the risk of ventilator-associated pneumonia by 30%, but closer inspection of the studies included in this analysis reveals that they each used a different probiotic. Additionally, none of the probiotics examined (i.e., Lactobacillus rhamnosus GG, Lactobacillus casei, and Lactobacillus plantarum 299) affected the risk of ICU-acquired infections.

Although there is an array of meta-analyses indicating that supplementing with probiotics can improve allergy-related and immunity-related outcomes, the results should be considered with caution because even in higher-quality meta-analyses that conducted subgroup analyses according to probiotic strain, there were almost never more than 2 or 3 studies that evaluated the efficacy of a specific probiotic strain or mixture of probiotic strains. Consequently, further research is needed to support the use of any specific probiotic 35

before they can be recommended, and probiotics/synbiotics are currently ranked as an unproven option. **How to take probiotics**

For readers who are not dissuaded by the limited body of evidence concerning the efficacy of specific probiotics for allergy-related and immune-related outcomes and are still interested in supplementing with probiotics, there appears to be 2 products that have more than 1 study behind them to indicate that they might confer a benefit, both of which are fermented dairy products.

Daily ingestion of 200 grams of a fermented dairy drink containing Lacticaseibacillus paracasei subspecies paracasei CNCM I-1518 or Lactobacillus casei DN-114 001 (marketed under brand names such as Actimel and DanActive) might reduce the risk of developing common infectious diseases.[140]

Daily ingestion of 7 grams of a powder containing cow’s milk fermented with Lactobacillus paracasei CBA L74 (providing 5.9x1011 colony-forming units of probiotic) might reduce the risk of developing a gastrointestinal tract infection.[142]

**N-Acetylcysteine (NAC)**

**What makes NAC an unproven option**

N-acetylcysteine (NAC) is derived from the amino acid L-cysteine. It is best known for its antioxidant properties, a consequence of its ability to directly scavenge some reactive oxygen species and the fact that it’s converted into L-cysteine after ingestion, which in turn is converted into the powerful antioxidant glutathione.[150][151] NAC also has anti-inflammatory and mucolytic (i.e., the ability to dissolve thick mucus and relieve breathing difficulties) properties.[150][151] The combination of these properties has generated interest in the use of NAC to improve allergy-related and immunity-related outcomes, particularly those related to oxidative stress and airway inflammation.

Evidence from a few randomized controlled trials indicates that in participants hospitalized with COVID-19, NAC did not affect the risk of in-hospital mortality or the need for mechanical ventilation, nor did it affect the length of hospital stay.[152][153] Given the small sample size, further research is needed to determine whether supplementation with NAC can improve clinical outcomes in people with COVID-19.

Similarly, evidence from a few randomized controlled trials indicates that NAC did not affect in-hospital or 30-day mortality in participants with acute respiratory distress syndrome or acute lung injury.[154] However, supplementation with NAC may reduce the duration of intensive care unit stay in this population. Again, due to a small sample size, confidence in these findings is weak, and further research is needed to determine the efficacy of NAC for improving clinical outcomes in people with acute respiratory distress syndrome or acute lung injury.

**Fish oil**

**What makes fish oil an unproven option** 36

Fish oil refers to two kinds of omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In the body, omega-3 fatty acids and omega-6 fatty acids serve as important constituents of cell membranes and influence the balance of anti-inflammatory and inflammatory signaling.[155] These fatty acids can be released from cell membranes and metabolized to produce eicosanoids. Eicosanoids are lipid-based molecules involved in modulating the intensity and duration of inflammatory responses, which in turn affects immune regulation.[156]

These physiological effects, in combination with the evidence demonstrating that maternal nutrition during pregnancy strongly influences the long-term health of the offspring — including immune system function[157] — have spurred interest in the potential of supplementing with fish oil during pregnancy to reduce the child’s risk of developing an allergy.

It’s thought that by increasing the intake of EPA and DHA from supplements and thereby increasing the content of omega-3 fatty acids in cell membranes, an anti-inflammatory milieu will arise that favorably modulates the immune system of the fetus and thus reduces the risk of developing an allergy during childhood.[158][159]

Despite the plausibility of this immune programming hypothesis, the available evidence collectively indicates that supplementing with fish oil during pregnancy does not affect the risk of the offspring developing an allergy during childhood (i.e., food allergy, eczema, asthma, allergic rhinitis).[160][158] Moreover, it does not appear that having infants supplement with fish oil reduces their risk of developing an allergy during childhood, either.[161]

**Stinging Nettle (Urtica dioica)**

**What makes Urtica dioica an unproven option**

Stinging nettle (Urtica dioica) is probably best known for the painful rash it produces when human skin comes in contact with the fine hairs on its leaves. Its recorded traditional medical use ranges from prostatic hyperplasia to arthritis, rheumatism, and allergic rhinitis.[162]

In view of its antihistaminergic effects and general anti-inflammatory properties,[163][164]it seems reasonable to assume that stinging nettle could at least ameliorate some of the classic symptoms of seasonal allergies like itchy eyes, nasal congestion, sneezing, and sinus pressure. However, clinical research that would prove or refute practically relevant real-world benefits is limited to only 2 randomized clinical trials with conflicting results.

The more recent and methodologically more thorough one of the 2 studies was conducted in Iran in 2017.[165]In the corresponding paper, the authors did report statistically significant reductions in nasal swab eosinophil counts and serum levels of interferon gamma, suggesting a calming effect on the overreacting immune system of the participants, which seems to be in line with a significant reduction in symptom scores on the Sino-Nasal Outcome Test 22 (SNOT 22)[166]. Upon closer scrutiny, these improvements did not differ between the participants who had received 150 mg per day of a commercial stinging nettle product for 4 weeks and those who had taken a placebo. This contradicts the more subjective assessment from a 1990 study in which the participants received 300 mg per day of freeze-dried stinging nettle from May to July (i.e., during the primary allergy season).[167]

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In the absence of a thorough statistical analysis of the significance of the inter-group difference and in consideration of the use of subjective interviews and marginally standardized allergy diaries as the sole outcomes of the study, it does make sense to place greater emphasis on the initially referenced null result of the Iranian study[166] and thus to classify stinging nettle as an “unproven” supplement option in the management of allergic rhinitis and related symptoms of seasonal allergies.

**Tinospora cordifolia**

**What makes Tinospora cordifolia an unproven option**

Tinospora cordifolia (TC), which is also known as gurjo, heart-leaved moonseed, guduchi or giloy, is a herbaceous vine indigenous to tropical regions of the Indian subcontinent. It has been used in Ayurvedic medicine for centuries to combat acute and chronic inflammation and is well known for its immunoregulatory properties,[168][169] which could also be used for the treatment of seasonal allergies.

However, the clinical evidence for the efficacy of TC in the treatment of allergic rhinitis and other symptoms of seasonal allergies is insufficient. Only a single randomized double-blind placebo-controlled trial studied the efficacy of T. cordifolia extract in participants with allergic rhinitis as its primary outcome.[170] The study, in which 75 participants diagnosed with allergic rhinitis were randomized to receive either a placebo or an aqueous extract of T. cordifolia stem thrice daily (3x300 mg/day) for 8 weeks, observed a highly significant reduction in sneezing, nasal discharge, nasal obstruction and itching in the treatment compared to the placebo arm of the study.

The treatment was well tolerated, and the reduction in eosinophil and neutrophil counts, the absence of goblet cells in the participants’ nasal smears, and the increased number of leukocyte numbers and cytological results all correlated with the previously reported clinical benefits of supplementation, implying that T. cordifolia may indeed serve as a natural remedy for people with allergic rhinitis. With only one study in direct support of TC's use as an antiallergic agent, T. cordifolia must yet still be considered an “unproven supplement”, the safety of which has recently come under scrutiny after a growing number of case reports from India seemed to suggest a link between its increasingly prevalent use during the COVID-19 pandemic and often severe drug-induced autoimmune-like hepatitis.[171][172]

In response to the publication of a paper documenting 6 cases of drug-induced autoimmune-like hepatitis in 2021,[171] there have been concerns about the potential hepatoxic effects of T. cordifolia supplements on the Indian market. As of now, it is not clear how warranted these concerns are, but in the absence of previous reports of TC-induced liver damage, and considering the widely held belief among Ayurveda practitioners regarding the safety of Tinospora cordifolia, scientists from the SRM Institute of Science and Technology in Chennai, India, speculated that the liver-damaging effects described in the 2021 case report could be a result of impurities or contamination of the products that individuals had used.[173] After all, the botanical authenticity of the supposedly TC-containing products had and still has not been investigated. However, with several additional case reports and a number of comments published in 2022 and 2023, the safety of commercially available TC supplements remains a matter of ongoing debate chiefly among Indian researchers.[172][174][175]

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**Bromelain**

**What makes Bromelain an unproven option**

Bromelain is a protein-digesting enzyme mixture derived from the stem, fruit, and juice of the pineapple plant. In Central and South America, the complex mix of protein-breaking proteases has a centuries-long history of use in treating various medical ailments. Bromelain possesses anti-inflammatory, antithrombotic, and anticancer activity in vitro.[176] Bromelain has also been shown to exhibit potent immunomodulatory effects.[177] Pertinent clinical applications of Bromelain include the treatment of allergic sensitization, (auto- )immune diseases, and viral infections. Unfortunately, the number of relevant clinical trials for each of these potential applications is limited, to say the least.

Many of the existing trials used bromelain as one of several pharmacologically active chemicals in a complex ingredient blend. Others focused exclusively on bromelain's effects on various markers of immune (re-)activity. These studies confirmed the ability of orally administered bromelain to modulate important markers of the cellular immune response in individuals without known health conditions.[178][179] However, they cannot confirm or refute the previously reported hypothesis about the supplement's clinical efficacy. A 2021 paper written by Iranian scientists from the School of Medicine at the Tehran University of Medical Sciences seems to be the only documented and published randomized, double-blind controlled clinical trial to investigate the effects of bromelain alone in a clinical context.[180]In this trial, 40 participants who were previously hospitalized with mild to moderate symptoms of COVID-19 were randomly allocated to receive either 200 mg of bromelain every 8 hours (600 mg/day, in total) or a placebo. In the first 72 hours to 120 hours of the 5-day intervention, the O2 saturation, as well as the respiratory and heart rate, of the participants in the treatment group recovered at a significantly higher pace compared to these measures in their peers in the placebo arm of the study. In conjunction with significant improvements in markers of immune, kidney, liver function, and inflammation, the results of the study are promising, but taken on their own, they are ultimately of little significance.

With only one study in support of tangible real-world benefits of bromelain supplements in the treatment of viral infections, and considering the complete lack of pertinent research on other (auto-)immune-related disease states (like seasonal allergies or viral infections), it should be obvious that bromelain falls into the overcrowded category of hypothetically promising practically but “unproven” immunoregulatory supplements.

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**Inadvisable Supplements**

**Tinospora crispa**

**What makes Tinospora crispa an inadvisable option**

| **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. |
| --- |

Tinospora crispa, not to be confused with Tinospora cordifolia,[181]is an herb traditionally used in Ayurvedic medicine.

There is no human evidence evaluating Tinospora crispa for any condition covered in this guide, and as such, it’s unproven. It may also be dangerous.

Data on the toxicity of Tinospora crispa in humans are limited. However, in 5 clinical trials and one case report, enzymes used as indicators of potential liver damage (AST and ALT) were elevated in some of the participants who were taking Tinospora crispa.[182][183][184][185][186] These markers returned to normal after treatment was stopped. Such elevations have been seen in animal studies as well. Additionally, there are open questions about the effects that Tinospora crispa may have on cholesterol because it might cause an increase.[183]

Because current evidence has not shown a benefit of Tinospora crispa for immune function and there is some evidence it may be harmful to the liver or cholesterol levels, this herb should not be supplemented.

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**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, should there be 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.

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**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. Can I take garlic and vitamin C in one dose instead of three?**

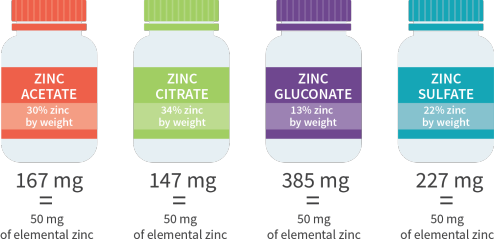
Water-soluble vitamins taken in excess are readily excreted. Smaller doses of vitamin C are more easily assimilated and stored (for a few days). Similarly, frequent dosing allows the bioactive compounds in garlic to remain longer in your body. This makes splitting your daily dose more effective, but not to a very great extent in either case, so if you can only manage a single dose per day, you’ll still benefit.

**Q. What’s the difference between elemental zinc and other kinds of zinc?**

“Elemental” refers to the weight of the mineral by itself, separately from the compound bound to it. For instance, consuming 50 mg of zinc acetate means consuming 15 mg of elemental zinc. Product labels display the elemental dosage. On a label, “15 mg of zinc (as zinc acetate)” means 15 mg of elemental zinc (and 35 mg of acetic acid).

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**Four different compounds of zinc**

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**Q. A lot of spirulina is farm-grown and harvested. How do I know it is safe?**

Spirulina is considered a food grade product and is generally rigorously tested. For example, it undergoes microbiological and chemical composition tests as well as tests for contaminants like heavy metals, pesticides, and extraneous materials.

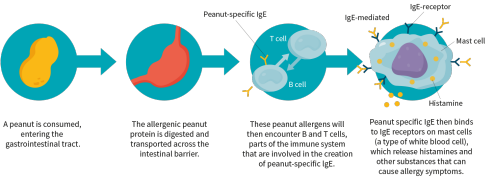
That being said, here’s a list of steps you can take to find a high quality spirulina supplement.

**Q. Is there anything to help with peanut allergies?**

Despite an increase in the number of mothers avoiding peanuts and other common allergy triggers during pregnancy and breastfeeding, the prevalence of peanut allergies actually increased since 1997.[187] About 4.4 million people in the U.S. now have allergies to peanuts,[187] and peanut allergies remain one of the deadliest food allergies.[188]

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**How peanuts cause allergic reactions**

****Reference: Burks. J Clin Invest. 2003.[189]

There is evidence that introducing infant-safe forms of peanuts (e.g., pureed into a smoothie) can reduce the risk of peanuts allergies. Timing depends on the risk level of the infant, with the highest-risk infants being introduced to peanuts at 4–6 months, with later introduction for lower risk infants.[190][191][192][193][194]

In short: infants at risk for developing peanut allergies who avoided peanut consumption were five times as likely to actually develop the allergy, compared to infants who consumed a peanut product at least three times per week through age 5.[191][192]

But what if you’re not an infant?

Fortunately, a medication recently approved in the United States can help temper the consequences of accidental peanut exposure in this group of children. The drug’s brand name is Palforzia. It’s the first drug approved by the United States Food and Drug Administration for any food allergy, and is indicated for children with peanut allergy aged 4 to 17. However, it can also continue to be taken into adulthood if started in childhood. It doesn’t cure peanut allergy; instead, it mitigates the allergic reaction to peanuts upon accidental exposure. However, children taking Palforzia should still avoid peanuts.

Palforzia is made of pharmaceutical-grade powdered peanut allergens that can be sprinkled into semi-solid foods like applesauce and yogurt. However, you can’t just pick it up in your local drug store, take it home, and use it. It’s only available in specific, licenced locations and patients have to enroll in a special program in order to get the drug. That’s because, while it’s effective, it does run the risk of inducing a serious allergic reaction.

While Palforzia treatment requires some monitoring in order to maximize safety and not all children can tolerate it, there’s good evidence to suggest that it’s effective in those children who can tolerate it.[195] Around 66% of children who were highly allergic to peanuts and who reached the maintenance phase after escalating their Palforzia dose could tolerate eating 600 mg of peanut protein (roughly equal to a couple of peanuts), compared to only 4% of children in the placebo group.

The study also included some adults, but there was no statistically significant effect in this age group, which is why Palforzia is only currently approved in children, with the option to continue it into adulthood.

While Palforzia isn’t a cure for peanut allergies, and children on the drug still have to avoid peanuts, it’s a major step forward in lowering the risk of a serious allergic reaction to accidental peanut exposure.

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**Q. Do any supplements protect against COVID 19?**

Some supplements have evidence for prevention or symptom reduction for the flu or the common cold — nobody knows how well this evidence applies to COVID-19 (if at all). If you opt to supplement with any supplements, including the ones mentioned in this guide, remember that none of them have proven efficacy against COVID-19. Harm from supplementation is especially possible with COVID-19 due to unknowns surrounding this virus and its manifestations.

Supplements are not strictly necessary, and they pale in comparison to established preventative measures.[196] Maintaining proper hygiene should be your primary focus, as it is the proven option for reducing the risk of spreading or contracting SARS-CoV-2.

Don’t let supplements lure you into a false sense of security. If you suspect you have COVID-19, do not rely on supplements as a cure or treatment — contact a healthcare professional.

That being said, The International Society for Immunonutrition (ISIN) has published a position statement on nutrition, immunity, and COVID-19. For the elderly specifically, it recommends increasing the daily intake of the following nutrients:

Vitamin C: 200–2,000 mg

Vitamin D: 400–4,000 IU (10–100 mcg) if low blood levels

Vitamin E: 134–800 mg

Zinc acetate: 30–220 mg

Importantly, they make the following disclaimer:

“There is no specific evidence these nutritional measures can help protect against, or even lessen the effects of, COVID-19 infection.”

Let’s add that the higher end of their zinc intake range (220 mg) far exceeds the established Tolerable Upper Intake Level (UL) of 40 mg/day.[51] Taking too much zinc for too long can be toxic and cause copper deficiency.[16][17] Do not exceed the UL for zinc for more than 2 weeks unless under the direction and supervision of a physician.

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