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January/February 2024

FEATURE ARTICLES

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PLUS, page 64:
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* *Gerontology.* 1996;42(3):170-80.

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ON THE COVER

Improve Sleep Efficiency

Clinical studies show that two plant extracts promote restful sleep. One improved **sleep efficiency** by **74%** while the other enhanced **restorative sleep** by **72%**.

DEPARTMENTS

LIFE EXTENSION®

The Science of a Healthier Life®

January/February 2024

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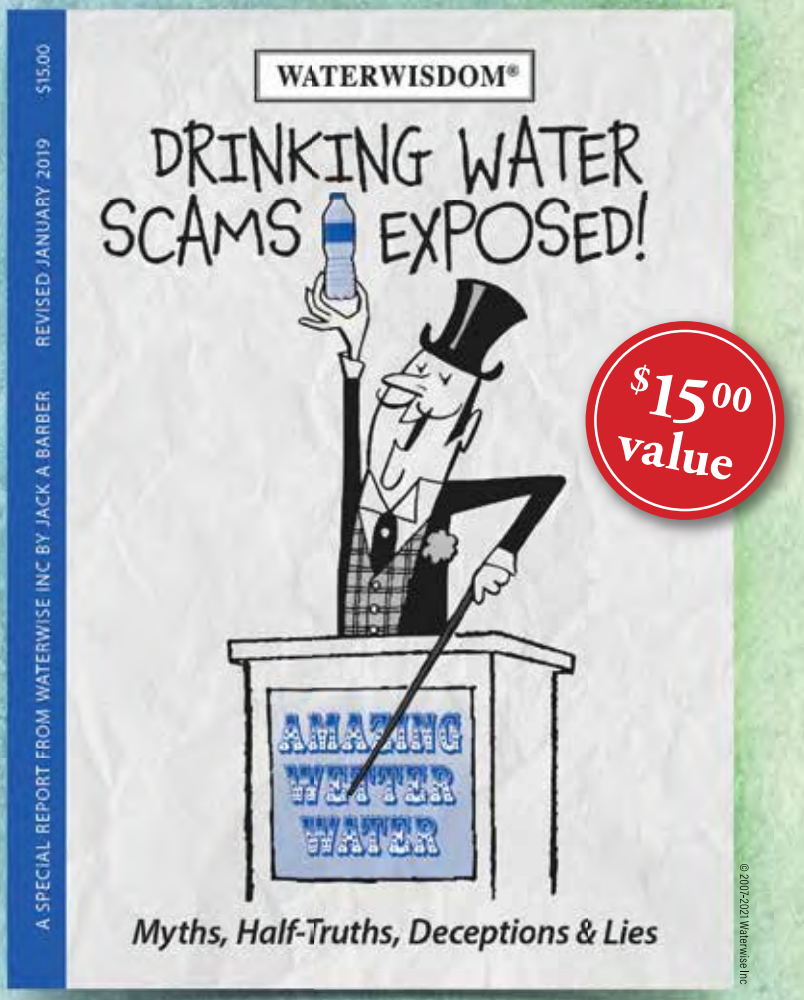

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Sandra C. Kaufmann, MD, is a fellowship-trained and board-certified pediatric anesthesiologist as well as the Chief of Anesthesia at the Joe DiMaggio Children's Hospital in Hollywood, Florida. She is the founder of The Kaufmann Anti-Aging Institute and the author of the book The Kaufmann Protocol: Why we Age and How to Stop it (2018). Her expertise is in the practical application of anti-aging research.

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In the News

Just Over Half a Tablespoon of Olive Oil Daily May Lower Dementia Death Risk 28%

A new study suggests that regular olive oil consumption may lower the risk of dying from dementia.

The study findings were presented at NUTRITION 2023, the flagship annual meeting of the American Society for *Nutrition*.*

Participants included 60,582 women enrolled in the **Nurses' Health Study** and 31,801 men in the **Health Professionals' Follow-Up Study**, between 1990 and 2018.

Every four years individuals responded to questionnaires providing information about foods they ate, including olive oil and other fats.

During more than 28 years of follow-up, there were 4,749 deaths from dementia. Consuming more than **seven grams** per day of **olive oil** (just over half a tablespoon) was associated with a **28%** lower risk of fatal dementia compared to consuming it rarely or not at all.

Editor's Note: "The lower risk of dementia mortality with olive oil intake was independent of overall diet quality, suggesting unique brain health benefits of olive oil,"
the study found.

* https://neurosciencenews.com/olive-oil-dementia-23678/

Some Heartburn Medication Found to Increase Dementia Risk

Long-term use of proton pump inhibitors (PPIs) has been associated with an increased risk of dementia later in life, according to a study published in *Neurology*.*

PPIs are drugs used to treat heartburn and acid-related disorders that work by reducing stomach acid production.

Using data from the Atherosclerosis Risk in Communities Study from 1987 to 2017, researchers evaluated the use of PPIs with dementia risk in 5,712 dementia-free participants, (mean age 75.4±5.1 years).

Results showed that using PPIs for more than **4.4 years** was associated with a **33%** increased risk of **dementia** later in life, compared to individuals who didn't use PPIs.

Editor's note: "PPIs were dispensed over 115 million times in 2016," the authors noted.

* *Neurology*. 2023 Aug 9:10.1212.

High Antioxidant Intake Lowers Risk of Gout

A study found a reduced risk of gout among men and women with a high antioxidant intake in comparison with those whose intake was low.*

Participants included 26,117 adults aged 40 to 59 enrolled in the National Health and Nutrition Examination Survey cycles from 2007 to 2018. Questionnaire responses were evaluated for the intake of the antioxidants selenium, zinc, vitamins A, C and E, and the carotenoids, to calculate the **composite dietary antioxidant index** (CDAI).

Men and women whose CDAI was among the top **25%** had an adjusted **35%** lower risk of gout than those whose CDAI was among the lowest **25%**.

Oxidative stress, which is decreased by antioxidants, and inflammation, have been found to be higher in gout patients than in those without the disease.

Editor's Note: Gout is a type of inflammatory arthritis caused by elevated uric acid that leads to the formation of painful sodium urate crystals in joints, tendons and surrounding tissues.

* *Biol Res Nurs.* 2023 Aug 24:10998004231198166.

Statins May Reduce Risk of Cardiovascular Disease in HIV Infection

Statins could reduce the risk of cardiovascular disease in individuals with human immunodeficiency virus (HIV) infection, according to a study funded by the National Institutes of Health and published in the *New England Journal of Medicine*.*

The study included 7,769 people with HIV, averaging 50 years old, who had a low-to-moderate risk of cardiovascular disease and were receiving antiretroviral therapy.

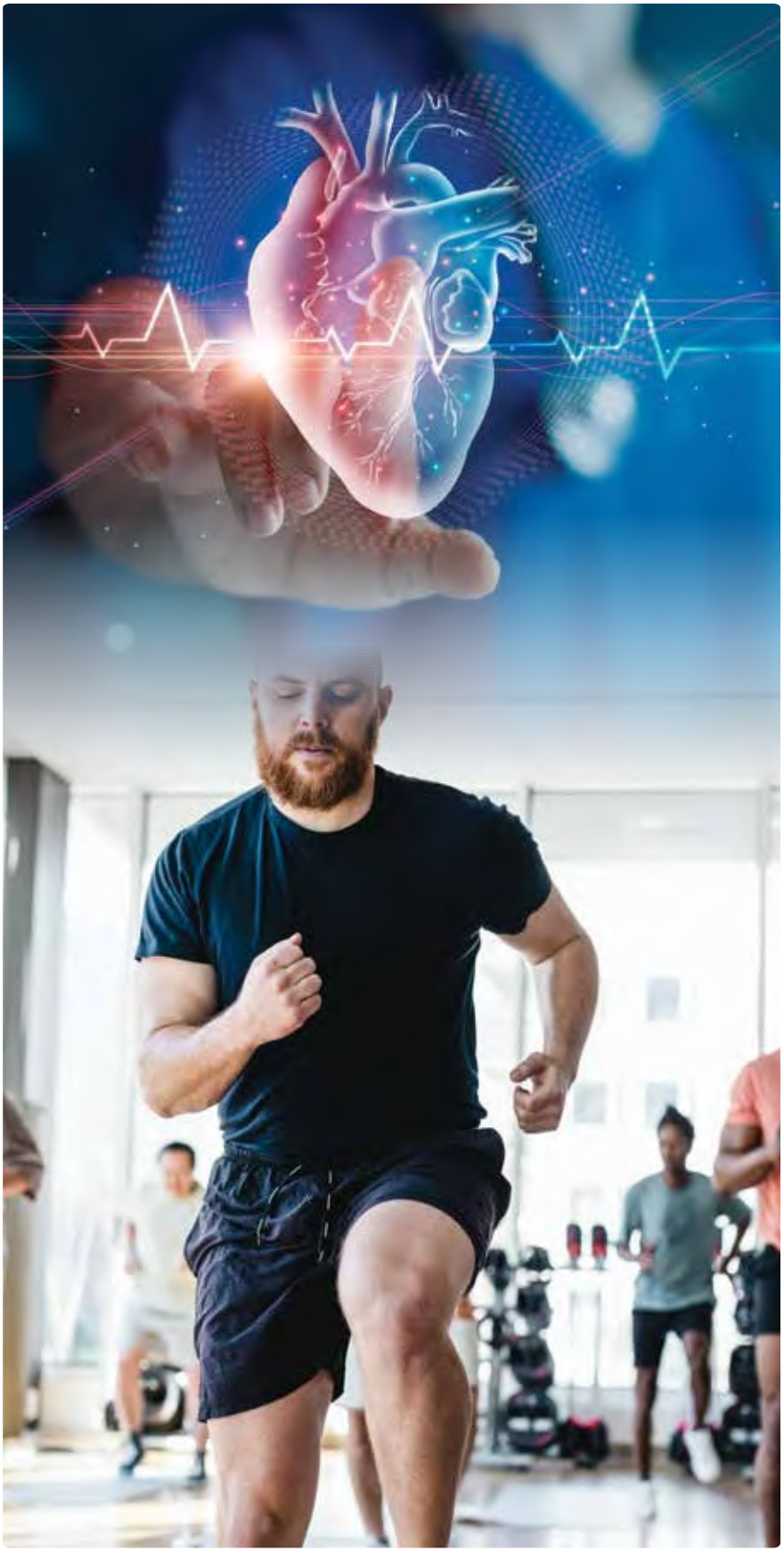
Participants took either a placebo or **4 mg** per day of **pitavastatin calcium** (a statin drug).

Researchers tracked the occurrence of major cardiovascular events such as myocardial infarction, stroke, peripheral arterial ischemia, or cardiovascular death.

After 5.1 years, there was a **35%** lower risk of a major cardiovascular event in the pitavastatin group, compared to the placebo group.

Editor's Note: The statin group also experienced a **30%** reduction in LDL cholesterol. Statins also have **anti-inflammatory** properties that can help reduce cardiovascular risks.

* *N Engl J Med.* 2023; 389:687-699.



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Protect TELOMERES from Premature Shortening

BY MARK FIELDS

In **March 2023**, the *Wall Street Journal* reported on a study showing that people over age 60 with **shorter telomeres** were **three times** more likely to die from **heart disease** and **eight times** more likely to die from **infections**.[1]

Shortened **telomeres** are associated with accelerated **aging** and higher risk of all-cause **mortality**.[2]

For decades, scientists have searched for ways to slow the shortening of **telomeres**.

An easy way to reduce the progression of telomere shortening has now been discovered.

Results of a **clinical study** showed that, in those who took a **selenium-CoQ10** combination for four years, there was a remarkable **49%** lower rate of death due to **cardiovascular** causes compared to **placebo**.[3]

A recent sub-study utilizing data from these participants was published in the medical journal *Nutrients*. Scientists found that the combination of **selenium** and **coenzyme Q10** significantly reduced the attrition of **telomeres** in subjects' cells.[4]

This is a potentially game-changing development and adds evidence to the benefits of **selenium** and **coenzyme Q10**. Halting telomere shortening, on top of the known benefits, would be huge.

Most readers of this magazine have supplemented with CoQ10 and selenium for many decades.

What Are Telomeres?

Telomeres are protective caps for your genetic material. Every **chromosome**—long, elaborately folded strings of DNA found in every cell—has telomeres on both ends. They help shield the **DNA** structure and keep the genetic material stable.[2,5]

Early in life, telomeres tend to be long and healthy. But with time, as cells age, telomeres **shorten**. When they become *too* short, the chromosomes are prone to damage and dysfunction. This causes cells to age and eventually die.[5,6]

Scientists have shown that longer, intact telomeres are associated with excellent cellular health, and may be associated with **longevity**. On the other hand, shortening of telomeres is associated with **aging** and chronic disease.[2,6,7]

For these reasons, the **prevention** of **telomere shortening** is a major interest of **anti-aging** research.

Selenium and CoQ10

Selenium is a trace mineral and is essential to the proper function of certain **enzymes**, specifically those involved in defense against oxidative stress and the damage it causes to proteins and cellular DNA.

Many older adults have *low* selenium levels.[8] Observational studies have shown low levels of selenium are associated with increased risk of **cardiovascular disease**.[9]

Coenzyme Q10 (CoQ10) is a lipid-soluble antioxidant naturally found in every cell of our body. It is critical to the health of **mitochondria**, cellular powerhouses that supply the energy cells need to survive and function.[10] After age 20, production of CoQ10 begins to *drop*, and older people often suffer from inadequate levels.[10,11]

Although selenium and CoQ10 play distinct roles in promoting health, they have an intimate connection. In other words, they are better together.

As **CoQ10** provides energy to the body, it becomes *inactive*. One of the enzymes that can convert the inactive CoQ10 back to the *active* form—called **ubiquinol**—*requires* **selenium**.[10]

At the same time, CoQ10 is required for selenium to be properly incorporated into essential body proteins.[12]

Impede Telomere Shortening

Several trials in the past have assessed the impact of selenium and CoQ10 on mitochondrial, cardiovascular, and metabolic health.

One such trial was of 675 older adults with low selenium levels who were randomized to receive either a placebo or a combination of **200 mcg** of selenium and **200 mg** of **coenzyme Q10** for four years. A significant reduction in cardiovascular mortality was seen in the treatment group as compared to placebo.[11]

A recent sub-study of this trial was conducted, and **telomere length** of those in the earlier study evaluated.[4]

In the **selenium-CoQ10** group, the rate of **telomere shortening** was **significantly reduced** compared to placebo.

While telomeres in the **placebo** group continued to shorten, the average length in **selenium-CoQ10** users was stable or even slightly *increased*.

The ability to halt telomere shortening over a four-year period in elderly adults is an extraordinary finding. Even more impressive is that, in this study, shorter telomeres were associated with more cardiovascular disease and a shorter life, while selenium and CoQ10 supplementation preserved telomere length and resulted in less cardiovascular death.

Better Heart Health

A clinical trial found that older people who took a combination of selenium and coenzyme Q10 for a period of four years experienced a lower rate of **death** due to **cardiovascular causes** (including heart attack, stroke, and heart failure), which was reduced by more than half.[12]

Researchers continued to collect data from participants, and results of two subsequent sub-studies have been consistent in regard to cardiovascular mortality.

Ten years after the end of this trial, the selenium-CoQ10 group was still **49%** less likely to die from cardiovascular causes.[11]

Even 12 years after the end of the treatment period, the benefit persisted. A **41%** lower risk in the active treatment group, as compared to placebo, was found in the second follow-up analysis.[13] These benefits remained when looking at subgroups who had preexisting conditions, including heart disease, diabetes, and high blood pressure.

Summary

A study of elderly adults has demonstrated that taking **selenium** and **coenzyme Q10** can impede telomere shortening.

Telomeres protect genetic material in cells. Their shortening is associated with increased risk of disease and death.

Protection against telomere shortening in those receiving the selenium-CoQ10 was accompanied by **lower rates of death** due to cardiovascular causes during follow-up of up to **12 years**. This was true even in those with preexisting conditions. •

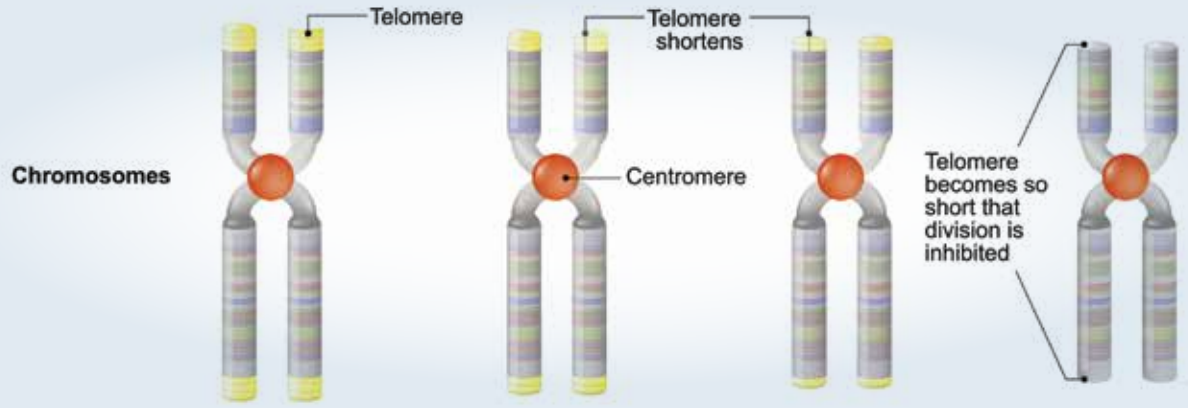
WHAT YOU NEED TO KNOW

Preserve Telomeres and Reduce Cardiovascular Death

- **Telomeres** protect the genetic material in every human cell. With aging, they tend to shorten, and this change is associated with increased risk for chronic disease.
- A study in older adults with low selenium found that oral intake of **selenium** and **coenzyme Q10 (CoQ10)** could slow or stop the shortening of telomeres over a four-year study period.
- Those receiving the treatment had significantly **lower rates of death** due to cardiovascular causes during a follow-up period of **12** years.

THE WALL STREET JOURNAL. March 12, 2023[1]

- The ***WSJ*** cited several studies associating **telomere length** with health outcomes in older people.
- Shorter **telomeres** were associated with **depression** and **cognitive** problems in people aged 60-79.
- People over 60 with shorter telomeres were **three times** more likely to die from **heart disease** and **eight times** more likely to die from **infections**.
- "Smoking, excessive drinking, pollution, stress, social isolation and eating processed foods…causes telomeres to **shorten faster**."



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**BMC Complement Altern Med.* 2019;19:97.

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Reduce Cartilage Loss in Osteoarthritis

BY LAURIE MATHENA

Osteoarthritis is the most common cause of joint pain, affecting more than 30 million adults in the U.S.[1]

Most standard approaches address its *symptoms*,[2,3] such as pain and stiffness.

But osteoarthritis damages and ultimately destroys the **cartilage** that allows the joint to function.[1]

Targeting only the pain and stiffness risks letting **cartilage damage** and **joint degeneration** continue *unabated*.

A novel solution may address not only pain and stiffness, but also underlying damage and destruction.

In two animal models, **three botanical extracts** demonstrated the ability to relieve pain and swelling and reduce **damage to cartilage**.[4,5]

Human studies have demonstrated that these plant extracts can provide symptomatic relief as well as benefits for joint structure.[6,7]

How They Work

Pain relief is the immediate goal of anyone suffering from osteoarthritis and the limitations it imposes.

But protecting against joint damage and improving joint **structure** is just as important.

Separate studies have shown that a combination of **Chinese skullcap**, **cutch tree**, and **white mulberry** tree extracts makes it possible to support *both*.

All three extracts help fight **inflammation** and maintain comfortable joints.

Cutch trees are rich in *catechins*,[8] compounds that inhibit pro-inflammatory signaling molecules. They suppress major pro-inflammatory molecules, such as COX-2, 5-LOX, and "master inflammatory promoter" **nuclear factor-kappa B (NF-kB)**.[7,9]

The root and bark of the **mulberry tree** are similarly rich in compounds with anti-inflammatory properties.[10,11]

Chinese skullcap (*Scutellaria baicalensis*) is rich in a compound called baicalin, with known anti-inflammatory properties that complement those in **cutch tree**.[4,12]

Reduced Joint Damage

Researchers conducted a randomized controlled clinical trial to compare two **non-drug** treatments to **placebo**.

This study enrolled 135 subjects aged 35-75 with mild to moderate **knee osteoarthritis**. Subjects had to have had symptoms for at least **six months** before the start of the study, and for at least 15 out of the previous 30 days at admission. They received one of three treatments for 12 weeks: [7]

1. **Cutch tree** and **white mulberry extracts** (**400 mg**/day),
2. Glucosamine (**1,500 mg**/day) and chondroitin (**1,200 mg**/day), or
3. Placebo.

The botanical extracts appeared to protect against **joint damage** and potentially **stop the progression** of the disease.

This was seen by measuring urinary levels of **C-terminal crosslinking telopeptide (CTX-II)**, a urinary biomarker of cartilage breakdown. *Higher* **CTX-II** levels in urine indicate *more* **joint damage**.

CTX-II rose sharply in the **placebo** group during the study (indicating additional joint damage), while there was little change in those taking glucosamine/chondroitin.

In the group taking cutch tree and white mulberry, there was a ***significant decrease*** in **CTX-II** levels.

This finding indicates that the plant extracts were protecting the joint against damage and could help reduce osteoarthritis progression over time.[7]

Clinical Study Shows Pain Relief

A randomized, placebo-controlled **90-day** trial in 60 subjects aged 40-75, with symptomatic osteoarthritis of the knee or hip tested the effect of a different herbal combination supplement, made of **Chinese skullcap** and **cutch tree**.

The patients were randomized to receive either a placebo, 200 mg/day of the drug celecoxib (Celebrex®), or one of two doses of the combination **herbal** supplement (**250** or **500 mg**/day of **Chinese skullcap** + **cutch tree**).

Subjects were followed-up for pain, stiffness, functional impairment, and physical function using standard measurement scales.[6]

Both doses of the dual-ingredient herbal supplement significantly reduced **pain scores** by the end of the 90 days.

Stiffness and **functional impairment** were significantly **reduced** in both herbal dosage groups, compared to baseline, and at all time points. These measures did not significantly improve in the celecoxib or placebo groups.

A measure of **physical function** significantly **improved** at all time points in the **herbal**-supplemented groups compared to **placebo**.[6]

Cartilage and Bone Protection

Animal and laboratory research confirms the results of the clinical trial that showed that the **cutch tree-white mulberry** combination preserves joint health.

An animal model showed that when used together, **cutch tree + white mulberry** reduced **cartilage breakdown** by nearly **55%** with a **41%** reduction in **sensitivity to pain** after five weeks.[5]

A similar animal model showed this same combination (cutch tree + white mulberry) resulted in an improvement in pain and **inflammation** much like that of a commonly used over-the-counter and pain medication, **ibuprofen**.[13]

Comparison to Common Medications

Many people suffering from joint pain turn to **nonsteroidal anti-inflammatory drugs (NSAIDs)**.

Unfortunately, this standard care manages only the symptoms,[2,3] such as pain and stiffness, overlooking damage to cartilage and bone.

A combination of **cutch tree** and **white mulberry** extracts was found in an animal study to be similar to ibuprofen in its ability to reduce pain and swelling.[14]

Chinese skullcap is also rich in anti-inflammatory compounds.

A blend of **Chinese skullcap** and **cutch tree** extracts was tested head-to-head against the drug **celecoxib** in people with severe knee osteo-arthritis.[6]

After 90 days, the cutch tree-Chinese skullcap blend was ***more effective*** than the drug at relieving pain, reducing stiffness, and improving physical function.

The combination was evaluated in animal and lab studies and has been shown to inhibit production and activity of inflammatory signaling molecules and significantly reduced pain and swelling.[4,15-17]

Summary

In addition to causing pain, stiffness, and loss of mobility, **osteoarthritis** causes progressive **cartilage damage** and **joint degradation**.

The three herbs—**Chinese skullcap**, **cutch tree**, and **white mulberry**—have been shown to reduce markers of inflammation, joint destruction, and cartilage degradation…indicating their potential to change the osteoarthritis landscape.

Studies indicate that combinations of these extracts are equal or superior to common medications at relieving pain, swelling, and stiffness.

As with any approach that offers prevention and relief of symptoms, the earlier you start, the better the long-term protective effect. •

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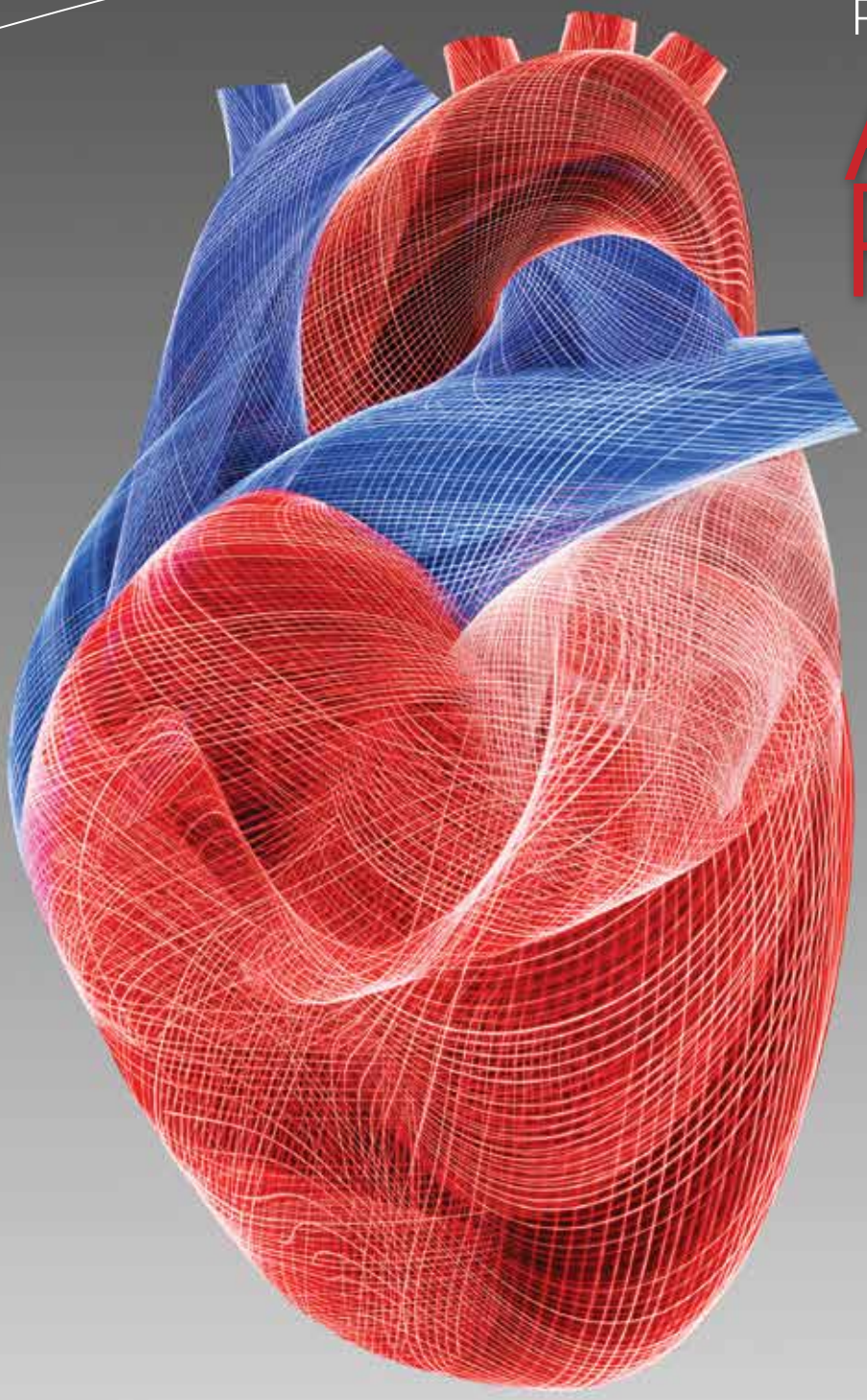

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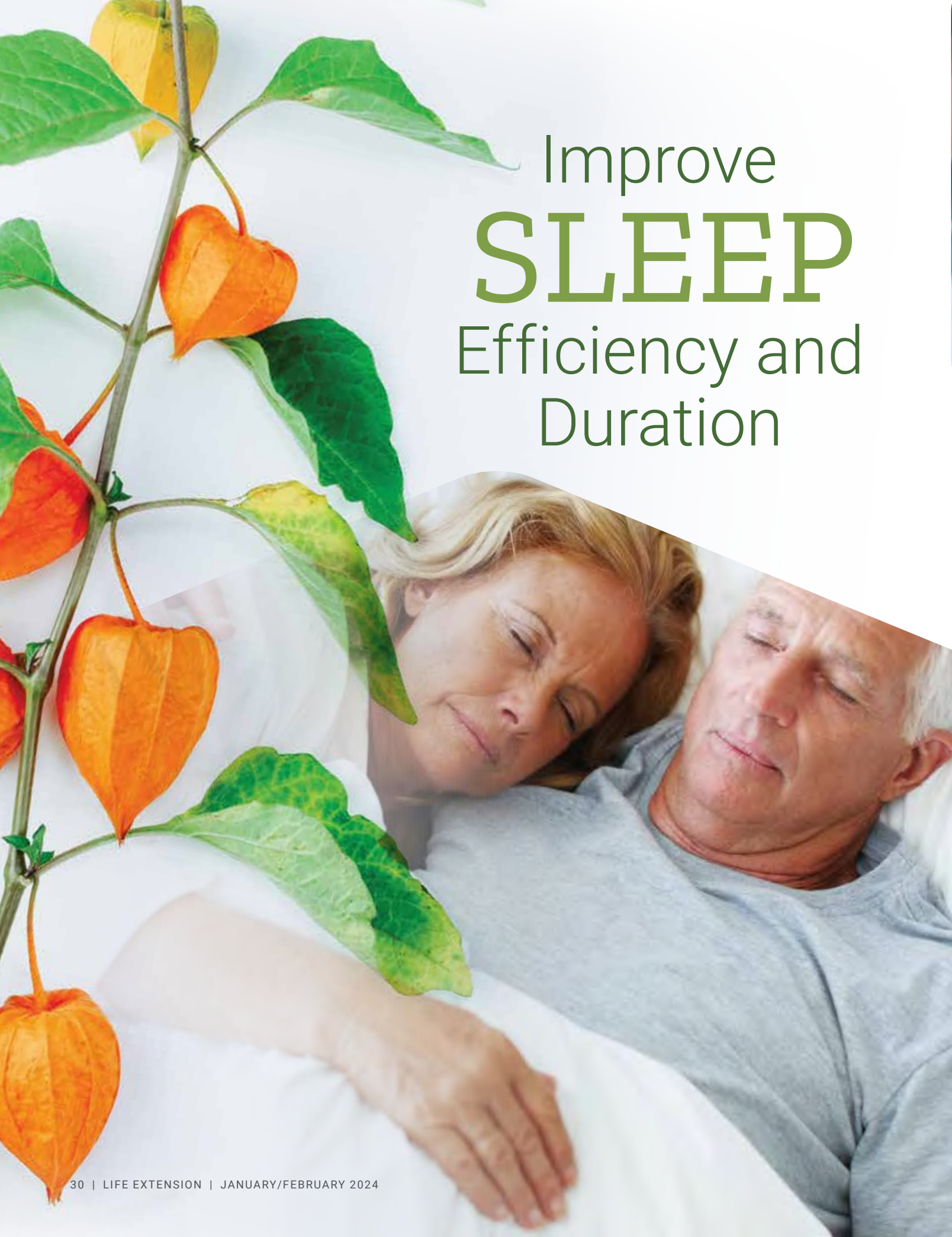
Improve SLEEP Efficiency and Duration



BY MICHAEL DOWNEY

Nearly a third of U.S. adults get less **sleep** than they should.[1]

Those who rely on **medications** confront **tolerance** whereby even *higher* doses fail to enable **restorative sleep**.

In an effort to improve sleep *without* drugs, researchers conducted randomized **clinical trials** on **plant-derived** extracts used in traditional medicine.

One of these extracts improved **sleep efficiency** by **74%**,[2] while another enhanced **restorative sleep** measures by **72%**.[3]

This article describes findings from **placebo-controlled** studies in sleep-challenged **humans**.

Sleep Deprivation and Human Longevity

Experts recommend that adults get ***seven or more hours*** of sleep each night.[1,4]

Yet around **40%** of elderly adults suffer from some form of sleep problem.[5]

For every **one-hour** reduction in sleep per night, there's about a **6%** increase in risk of **death** from any cause.[6]

Effects of Plant Extracts

Two extracts have been individually tested in randomized placebo-controlled clinical trials to promote deep, **restorative sleep**:

1) **Black cumin** is an herb long used in Indian and Arab traditional medicine. Its health properties come from the seed oil, which contains the active compound ***thymoquinone***.[7]

Scientists developed a **black cumin seed extract** standardized to **5% thymoquinone**, higher than other cumin extracts.

In a small pilot study of healthy subjects with sleep disturbances, it improved **sleep quality** and **duration**, and relieved stress and anxiety.[7] This result was confirmed in a larger trial in healthy people with self-reported unsatisfactory sleep (discussed later).[2]

2) **Ashwagandha** is an herb used for thousands of years in traditional Indian medicine that has been shown to have anxiety-reducing effects.[8-10] Its roots and leaves contain active compounds called ***withanolide glycosides***.[9]

One clinical trial showed that an extract standardized to **35% withanolide glycosides** lowered the stress hormone **cortisol**, which may help promote sleep.[11]

Clinical Trials with Black Cumin

A study published in **2023** enlisted healthy volunteers who reported **non-refreshing sleep**. This included waking multiple times nightly or being unable to achieve sound sleep.

Participants were given a placebo or **200 mg** of **black cumin extract** nightly, 20-30 minutes before bedtime. All subjects refrained from caffeine, alcohol, and tobacco.[2]

Beneficial effects were reported by **62%** of the black cumin group after a ***single dose***. This rose to an astonishing **88%** on day 90.

After **90 days**, compared to placebo, the **black cumin** users were evaluated using a validated self-reported sleep questionnaire. They reported not only better, longer sleep but also improved functioning during the day.

Researchers reported the following improvements of sleep parameters:[2]

- **74%** in sleep efficiency (time asleep out of total time in bed),
- **56%** in sleep latency (time needed to fall asleep after going to bed),
- **49%** in sleep quality,
- **45%** in daytime function,
- **22%** in sleep disturbance, and
- **20%** in sleep duration.

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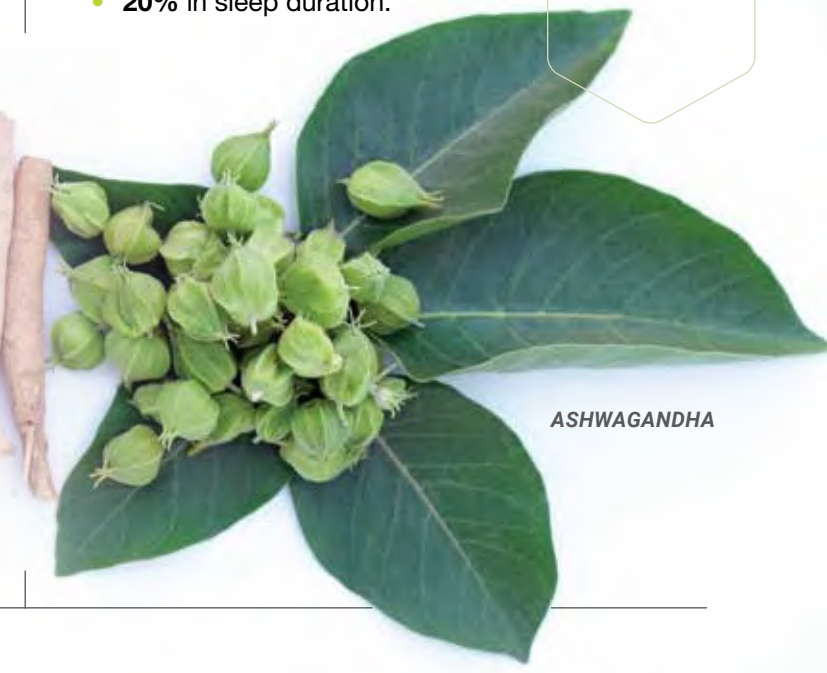

ASHWAGANDHA

Unlike those using prescription sleep meds, these people performed better the next day without drowsiness.

In a second trial, subjects with non-refreshing sleep took a placebo or **200 mg** of **black cumin** extract nightly, 10-30 minutes before bedtime.[12]

All participants wore an **actigraphy** wristwatch sensor that monitors rest/activity, a validated objective evaluation of sleep quality and duration.

After ***just seven days***, extract users had meaningfully improved their sleep duration, efficiency, and time to fall asleep, as evaluated by the objective actigraphy sensor. Compared to the placebo group, researchers reported improvements of sleep parameters:[12]

- **69%** in restorative sleep,
- **35%** in sleep latency, (amount of time to fall asleep),
- **23%** in time spent awake *after* sleep onset, (wakefulness time after defined sleep onset),
- **19%** in total sleep time, (from an average 6.4 hours to >7 hours, as recommended by the CDC), and
- **8%** in sleep efficiency (time asleep out of total time in bed).

Compared to the baseline there was **75%** improvement in **restorative** sleep in the group that received the extract. This specific **black cumin seed extract**, standardized to **5% thymoquinone**, safely promoted deeper, more healthful sleep.

Get Deep, Stress-Free Sleep

- Over a third of Americans get insufficient or poor-quality **sleep**. This increases the risk of many chronic diseases, including heart disease, dementia, and some cancers, and of ***all-cause mortality***.
- Clinical studies show that two plant extracts safely promote high-quality **sleep** and reduce **stress** and **anxiety**, *without* compromising daytime functioning.
- A **black cumin seed extract** improved sleep efficiency by **74%** and reduced the time needed to fall asleep by **56%**.
- An **ashwagandha extract** improved restorative sleep by **72%**, reduced stress by **62%**, and lowered levels of cortisol (the "stress hormone") by **67%**.
- Together, these extracts offer a **melatonin-free** choice for those seeking stress relief and a deeper, more restorative sleep.

Clinical Trials with Standardized Ashwagandha

To test an **ashwagandha extract** standardized to **35% withanolide glycosides**, scientists enlisted 150 volunteers suffering from non-restorative sleep. Half the subjects took a **placebo** and half took **120 mg** of **ashwagandha** each night for six weeks.[3]

All participants wore an **actigraphy** wristwatch that monitors rest/activity and evaluates sleep duration, efficiency, and latency.

Those taking **ashwagandha** had improvements of:[3]

- **72%** in restorative sleep,
- **27%** in sleep latency,
- **15%** in time spent awake *after* sleep onset,
- **5%** in total sleep time, and
- **5%** in sleep efficiency.

A second clinical study enlisted volunteers with moderate **anxiety** and elevated **cortisol**, which can lead to sleep issues. Participants were randomized to receive either ashwagandha **60 mg** or **120 mg**, or a placebo. Thay were evaluated at baseline and after 15, 30, 45 and 60 days.[13]

After 60 days, those taking **120 mg** of **ashwagandha** had:[13]

- **67%** reduced cortisol levels,
- **59%** reduced anxiety, and
- **62%** reduced stress.

Standardized to **35% withanolide glycosides**, this novel **ashwagandha extract** safely lowered anxiety and promoted more restful sleep.

Black cumin and ashwagandha extracts have been shown to improve parameters of **restorative sleep**.

Summary

Many Americans turn to medications to cope with poor sleep, but they come with side effects.

Two plant extracts have been shown to improve sleep onset, efficiency, and **total sleep time**, and reduce **anxiety** without compromising daytime function.

In clinical studies, a **black cumin seed extract** improved sleep efficiency by **74%** and perceived stress by **44%** – leading to improved daytime functioning.

An **ashwagandha extract** improved restorative sleep by **72%** and lowered stress by **62%**.

These **plant extracts** together provide an opportunity for more Americans to achieve healthy **restorative sleep**. •

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**J Diet Suppl.* 2021;18(4):387-405.

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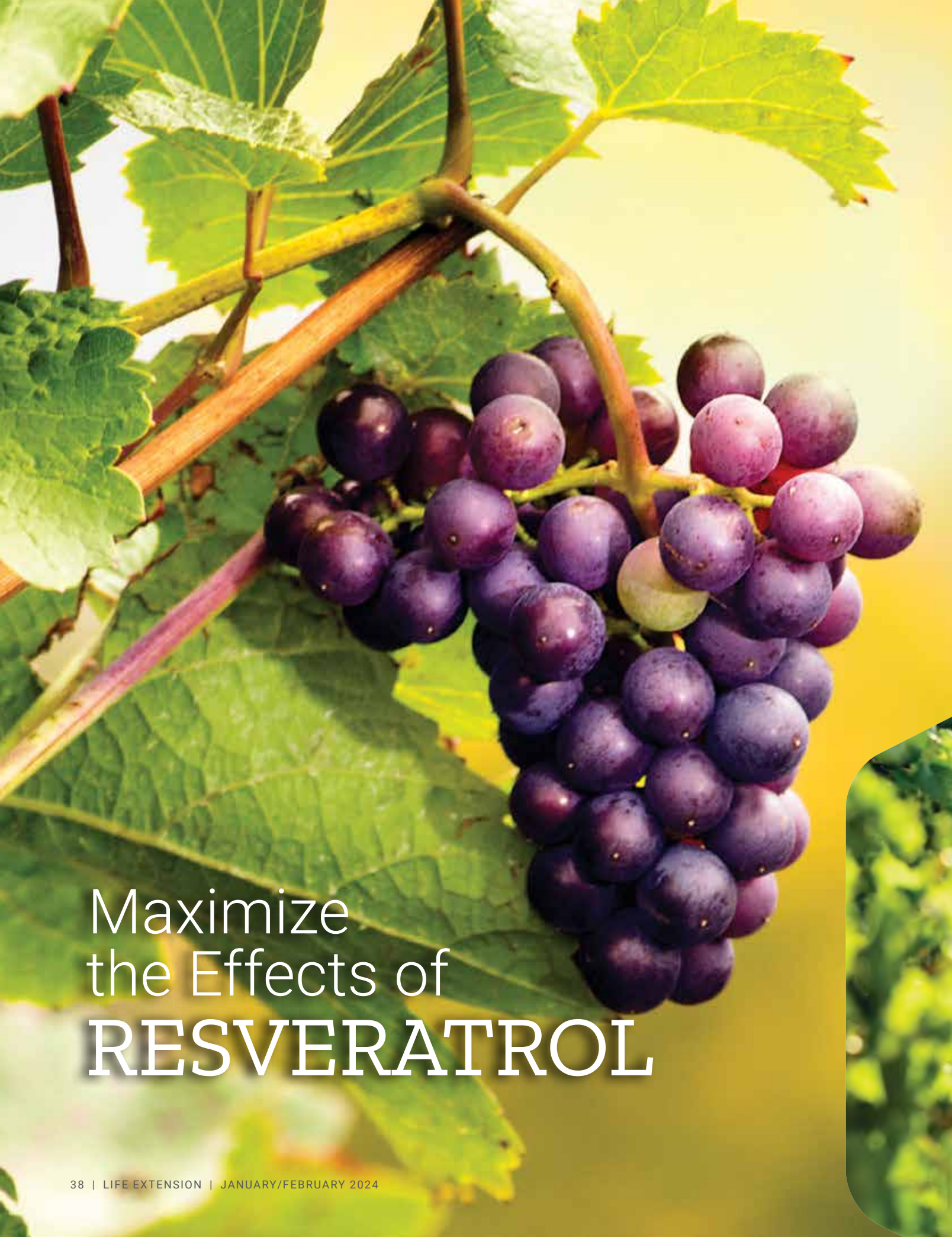


Maximize the Effects of RESVERATROL

BY JOHN JOHNSON

The potential of **resveratrol** to beneficially impact our health and longevity has been studied for many years.

Research in animals and cells has shown it can delay certain aging processes.[1-5]

Human studies of resveratrol over the past decade have shown its beneficial effects.[6,7]

Resveratrol, however, has poor **bioavailability**.

Scientists developed a formula that allows ***10 times*** as much resveratrol to make it to cells, where it can exert an array of benefits.[8]

With this innovation, it is thought that resveratrol can better combat the effects of aging.

Activating Anti-Aging Processes

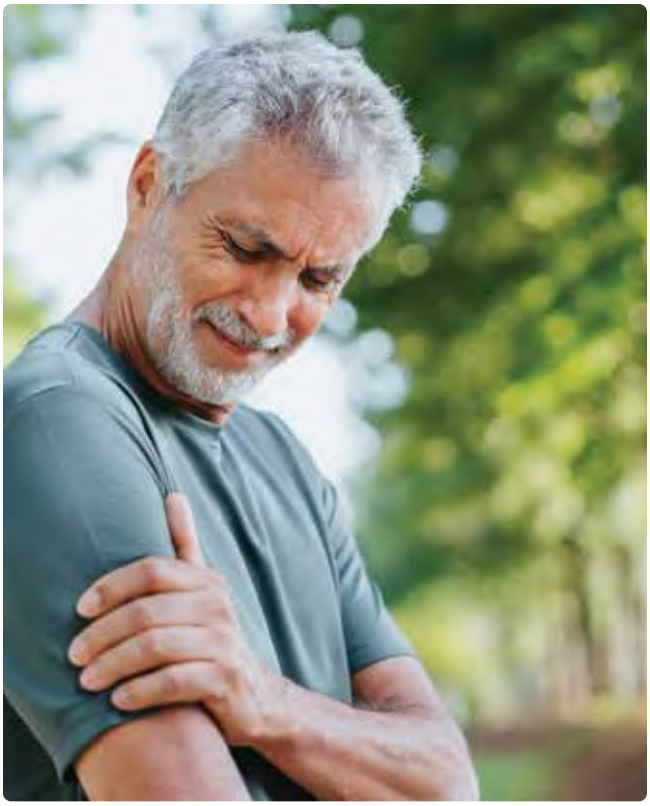
Resveratrol is a polyphenol compound found in red grapes, some berries, and several other plants.

Preclinical studies have shown that resveratrol activates multiple **anti-aging** processes.[1-3,5]

Some of the protective mechanisms demonstrated by resveratrol include:

- **Anti-inflammatory** support,
- Increased activity of **sirtuins**, cellular protector proteins linked to longer life,
- Improvements in **insulin sensitivity** and other areas of metabolic health,
- Preventing harmful changes to **DNA** associated with cellular dysfunction,
- Improved function of energy-generating **mitochondria**,
- Activating **autophagy**, cellular "housekeeping," and
- Promoting a healthy mix of microorganisms to improve **gut health**.

Resveratrol has demonstrated beneficial effects on all the above anti-aging factors.[1-3,5]



Extending Life

Resveratrol can exert body-wide protection to help protect the heart, muscles, bones, and kidneys.

It has also been shown to prolong overall life. In numerous studies of organisms from yeast to mice, resveratrol **extends lifespan**.[2,3,9]

For example, giving resveratrol to short-lived flies resulted in mean lifespan extension of up to **29%**.[9,10] In honeybees, it increased the maximum lifespan by **38%**.[11]

Because of the long lifespan of humans, it is difficult to evaluate a nutrient's ability to extend life in clinical trials. However, human studies do indicate that resveratrol can reduce major contributors to premature aging.

Fighting Metabolic Disease

Low **insulin sensitivity** and poor **glucose control** are major contributors to the aging process. They can lead to **type II diabetes** and increased risk for cardiovascular disease, cancer, and dementia.

Human trials show that **resveratrol** intake benefits **metabolic health** in adults with diabetes or other signs of metabolic disease. Doses from **150** to **1,500 mg** daily led to improvements in markers of healthy aging, including:[12]

- Increased insulin sensitivity and improvements in a marker of insulin function,[12-18]
- Better blood glucose control,[19] including lower levels of fasting glucose, post-meal glucose,[14,18,20] and glycated hemoglobin HbA1c (a marker of long-term blood sugar control),[12,15-19,21]
- Reduction in markers of nonalcoholic fatty liver disease,[17,20]
- Improved cholesterol levels,[16,21]
- Reduction in signs of oxidative stress[13,22] and markers of inflammation,[17,23,24]
- Increased sirtuin activity,[12]
- Lower blood pressure,[12,16,21] and
- Reduction in body weight, waist circumference, and body mass index.[15]

Being **overweight** or **obese** is associated with metabolic disease and contributes to rapid aging and risk for disease.

WHAT YOU NEED TO KNOW

In a clinical trial of diabetics (type II) participants on oral blood sugar medications were recruited. One group received **200 mg** of resveratrol daily for 24 weeks and another received a placebo. At the end of the trial, the resveratrol recipients had reductions in glucose and insulin, as well as reduced insulin resistance, compared to the beginning, and to the **placebo** group.[24]

In a double-blinded crossover trial of healthy obese men, with a four-week washout period, taking **150 mg** of resveratrol daily for 30 days resulted in beneficial changes to fat tissue, including ***decreasing the size of fat cells***.[17,25]

One human placebo-controlled study found that **1 gram** of resveratrol per day for **45 days**, compared to a placebo, provided antidiabetic effects in patients with **type I diabetes**, a lifelong condition with no cure.[22]

Not only did resveratrol improve metabolic health, but it also helped guard against complications of metabolic disease in a clinical trial of diabetics with foot ulcers.

For example, nonhealing **foot ulcers** are a frequent problem in those with type II diabetes. Resveratrol *increased* the healing rate. In a clinical trial of diabetics with foot ulcers **50 mg** of resveratrol two times per day for **60 days** promoted reduction in foot ulcer size in the treatment group as compared to placebo.[26]

Protect Against Accelerated Aging

- **Resveratrol** is a polyphenol found in red grapes and other plants. It helps defend cells against accelerated aging and risk for disease.
- In animal models and cell experiments, resveratrol was capable of significantly **extending lifespan**.
- In **human trials**, resveratrol countered many factors associated with rapid aging, including reducing oxidative stress and chronic inflammation, improving insulin sensitivity and glucose control, and enhancing heart function.
- Encasing resveratrol in a **hydrogel** of plant-derived fiber boosts its bioavailability by more than **10 times**.

In another trial, diabetics suffering from chronic **gum** and **tooth disease** who took **480 mg** resveratrol **per day for** four weeks had a significant improvement in periodontal status along with improved insulin sensitivity as compared to the **placebo**.[27]

Cardiovascular Benefits

Preliminary studies have shown that resveratrol can support metabolic health associated with cardiovascular disease risk. And it may protect against the development of **atherosclerosis** (buildup of plaque in arteries) and other **heart disease**.[7] Now, clinical studies are confirming these findings.

One clinical trial published in **2023** included 80 patients with high blood pressure who were randomized to receive either **400 mg** resveratrol or placebo for six months. Results showed that resveratrol protected the heart against **remodeling** (harmful changes in size and shape that affect cardiac functioning), while also protecting against left ventricular function **fibrosis** (scarring).[28]

In a double-blind, placebo-controlled trial, 40 heart attack patients were randomized to receive a **10 mg** resveratrol capsule daily for three months or a placebo. After three months the resveratrol group showed improved heart function, blood vessel function, and LDL cholesterol levels as compared to placebo.[29] Platelet aggregation, which can lead to abnormal blood clotting, was also reduced.

Better Bioavailability

Many researchers have long believed that resveratrol's effectiveness is limited by its poor **bioavailability**. The body's metabolism of unformulated resveratrol causes it to be rapidly cleared from the bloodstream and eliminated.

Scientists have discovered that encasing resveratrol in a **hydrogel** made of indigestible plant-derived fiber called **galactomannans** shields it from this process and makes it more bioavailable.

In a **human trial**, this hydrogel boosted the bioavailability of resveratrol by more than ***10 times*** compared to that of standard resveratrol.[8] That means **10 times** more resveratrol stayed in the bloodstream to get delivered to cells.

It also stayed in the bloodstream longer, with a **four-fold** greater half-life than standard resveratrol.

That may help resveratrol to fully achieve its many benefits throughout the body.

Summary

Resveratrol counters many of the factors that contribute to accelerated aging and risk for disease.

Animal models have shown that it **extends life** and reduces risk of disease.

Human trials have found that resveratrol improves insulin sensitivity, reduces chronic inflammation, helps protect the heart, and more.

Encasing resveratrol in a **hydrogel** of plant-derived fiber improves the **bioavailability** of this nutrient. •

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European Journal of Nutrition. 2011;50(5):387-389.

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- **Saffron**[3,4]
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- Promote lung function[2-4]

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Mg
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How MAGNESIUM & VITAMIN D Work TOGETHER

BY BRIAN MCKNIGHT

Magnesium[1,2] and **vitamin D**[3-5] are vital to overall health.

But if you're taking either one *alone*, you're not getting the full benefits.

Research has shown that these two nutrients rely on each other to provide systemic benefits.[6]

Magnesium is critical for converting vitamin D to its *active* form in the body and aids its transport in the blood.[7]

At the same time vitamin D promotes magnesium *absorption* in the intestines.[6,7]

Given their inter-reliance, taking them together is a sound nutritional strategy.

Observational studies show that both **vitamin D** and **magnesium** intake is associated with improved protection against insulin resistance, type II diabetes, and even death from any cause.

In **clinical studies**, taking both vitamin D and magnesium led to lower blood pressure, improved strength and muscle function, and reduced markers of **inflammation**.

Whole-Body Health

Magnesium is required for the function of 300-600 *enzymes* in the body.[1,6]

Magnesium deficiency has been tied to many common health conditions, including osteoporosis,[1] high blood pressure,[1,8] risk for cardiovascular disease,[1,8] metabolic disease,[1,2,8] cognitive decline,[8] and dementia.[8]

Vitamin D impacts a range of bodily functions. People with low levels of vitamin D have been found to have higher rates of cardiovascular disease,[3,5] dementia,[4] cancer,[3] bone thinning,[4,5] and more.[3-5]

Recent estimates show that as many as **50%** of all adults may have suboptimal **magnesium** levels[9] and over **40%** of adolescents and adults in the U.S. have low **vitamin D** levels.[10]

Working Together

These two nutrients are *not* independent. Inadequate intake of one can impact the levels and function of the other.

Here's how:[6,7]

- **Vitamin D supports intestinal magnesium absorption.** Vitamin D supports optimal absorption of magnesium in the intestines. If you consume oral magnesium but *don't* get enough vitamin D, your magnesium levels may remain low.

- **Magnesium is required for vitamin D activation.** Whether consumed or obtained by exposure to sunlight, vitamin D must be modified into its active form in the body to exert its beneficial effects. The *enzymes* that convert **vitamin D** to its active form *require* **magnesium** to function.

- **Vitamin D transport and delivery rely on magnesium.** Almost all vitamin D in the blood is transported and delivered to tissues by a protein called the **vitamin D-binding protein**. This protein also *requires* magnesium to function.

In short, inadequate magnesium compromises vitamin D activation and delivery.

And inadequate vitamin D compromises magnesium *absorption* and can contribute to low magnesium status.

If either nutrient is lacking, the other suffers as well. It's vital to get enough of *both*.

Benefits of Combined Intake

Over the last decade, *observational studies* have documented this interdependent relationship between **magnesium** and **vitamin D**, including how it relates to several common chronic diseases of aging.[11-14]

For example, *higher* **vitamin D** levels in the body are associated with a *lower* likelihood of insulin resistance, pancreas dysfunction, type II diabetes, high blood pressure, and **overall mortality**.[11-15]

Higher intake of **magnesium** has been shown to improve vitamin D levels.[16] It appears that magnesium may also allow the body to properly utilize vitamin D in order to protect against these chronic conditions.

In one large, observational study, those with *higher* levels of **vitamin D** had *lower* risk for **insulin resistance**, a condition that often leads to type II diabetes. **Magnesium** intake supports this association. That suggests that people with *higher* vitamin D levels and higher magnesium intake may have the *greatest protection* against insulin resistance.[15]

In a separate analysis of that same observational dataset, vitamin D was associated with better pancreatic beta-cell function, and magnesium helped strengthen this effect.[12]

An analysis of data from another large observational cohort (over 10,000 participants), showed that high magnesium intake was associated with a modest reduction in incidence of type II diabetes, compared to low magnesium intake. The analysis also found that better vitamin D levels helped strengthen this association.[14]

Another observational study found that elevated systolic **blood pressure** was associated with lower vitamin D levels. Higher intake of magnesium strengthens the protective effect of vitamin D against high blood pressure.[13]

Clinical Trials

Clinical trials have further confirmed the link between magnesium and vitamin D.

In one randomized controlled trial, oral magnesium supplementation successfully raised vitamin D levels in subjects with *low* blood vitamin D concentrations.[17]

Another double-blind, controlled trial in obese or overweight individuals found that the combination of both magnesium and vitamin D resulted in greater increases in blood levels of vitamin D compared to those who took vitamin D alone.[18]

In a similar study, healthy postmenopausal women were randomized to receive either **500 mg** of **magnesium** daily or a placebo.[16] At baseline, over **80%** of these women were vitamin D deficient. Taking magnesium resulted in a significant *increase* in **vitamin D** levels.

Placebo-controlled clinical studies have also explored how taking both **magnesium** and **vitamin D** can affect various areas of health, including:

- **High blood pressure.** In a study referenced above, in obese or overweight adults with elevated systolic blood pressure at baseline, taking **360 mg** of magnesium with **1,000 IU** vitamin D resulted in greater serum concentrations of vitamin D.

- **Mental health.** Magnesium and vitamin D have each been shown to benefit mental health, including anxiety and depression.[19-21]

- **Muscle strength and function.** In a clinical study, 83 healthy, middle-aged, vitamin D-deficient women were randomized to receive a combination of **50,000 IU** of **vitamin D** weekly and **250 mg** of **magnesium** daily for eight weeks, or placebo. Results showed that the vitamin D and magnesium group had a significant *increase* in **handgrip strength** and overall **mobility**, compared to the placebo group. The treatment group also had a *decrease* in an important inflammatory marker, compared to the beginning of the study.[22]

WHAT YOU NEED TO KNOW

Magnesium and Vitamin D Need Each Other

- Getting enough **magnesium** and **vitamin D** is critical to overall health. A deficiency in either is associated with increased risk for a wide range of chronic health conditions.
- Magnesium and vitamin D rely on each other. Studies have found that adequate levels of either one are necessary for the other to function properly and to reach optimal levels.
- In observational studies, taking both **vitamin D** and **magnesium** is associated with increased protection against insulin resistance, and better metabolic health.
- In clinical studies, taking both **vitamin D** and **magnesium** is associated with improved mental health, muscle strength, and blood pressure.

Together with a wealth of observational studies, these trials show the benefits of ensuring adequate intake of both vitamin D and magnesium.

Summary

Magnesium and **vitamin D** are inextricably linked. The levels of one impact the levels and function of the other.

The body needs magnesium to activate and transport vitamin D. In return, vitamin D can *enhance* magnesium absorption and retention.

Working together, **magnesium** and **vitamin D** can benefit musculoskeletal, metabolic, and heart health. •

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1. Akay Internal Study. Liposomal hydrogel vitamin C pharmacokinetics. Data on file. 2021.

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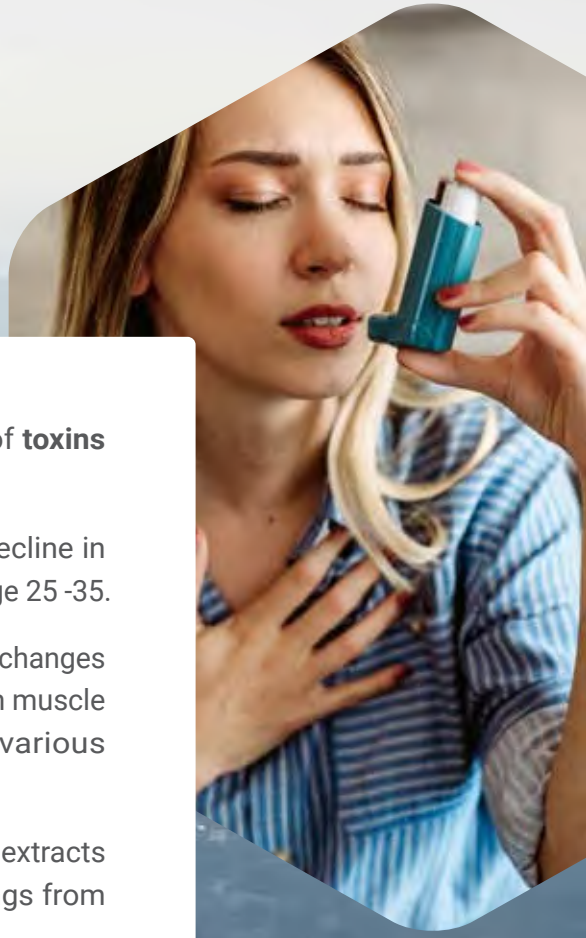
Protect LUNGS from POLLUTION

BY RICHARD EVANS



Our airways are exposed to a barrage of **toxins** that can cause chronic **lung diseases**.[1-3]

The lungs suffer an estimated **1%-2%** decline in function *every year* beginning at around age 25 -35.

This functional falloff can be attributed to changes to lung tissue and structure, to changes in muscle strength, as well as to exposure to various pollutants.[4-6]

Scientists have discovered plant-derived extracts and compounds that help shield the lungs from damage and boost respiratory function.

In a clinical study, a blend of two plant-derived compounds *increased* a measure of **lung capacity** by an astonishing **30%**.[7]

Lung Health Matters

People with the *best* lung function have a *longer* **lifespan** and **healthspan** (the duration of healthy living free from disease).[5]

Pulmonary function, however, tends to decline with age.[8]

An estimated **1%-2%** of lung function is lost *per year* beginning around age 25-35.[8,9] That decline contributes to frailty and deteriorating physical fitness.[6,10,11]

Another reason that lung function deteriorates with age is air **pollution** that injures the delicate tissues of our respiratory tract.

More than **40%** of Americans live in areas with **poor air quality**. In recent years, some areas have experienced a worsening in air quality at certain times of year with increased exposure to **wildfire smoke**.[12]

Poor air quality is associated with deteriorating lung function and *higher* risk for lung problems, including:[5,13,14]

- Asthma,
- Emphysema,
- Bronchitis,
- Lung infections, and
- Lung cancer.

To address the threats that aging, and pollution pose to respiratory health, scientists investigated several **plant-derived** extracts and compounds that have been shown to protect the lungs and improve lung function.

Boswellia-Bael Fruit Blend

Boswellia serrata is a tree native to parts of Asia that has long been used in traditional Indian medicine.[15] It has been shown to have benefits for respiratory disorders such as asthma.[15,16]

Bael fruit is native to India and other parts of Asia. This fruit and its seeds have been used in traditional medicine for a range of disorders.[17]

Scientists combined extracts of **Boswellia** resin and **bael fruit** and tested them in **clinical trials**.

In one study, healthy adults who reported a sensitivity to air pollution received either **200 mg** daily of **Boswellia-bael fruit** blend or a **placebo**.[7]

After three weeks, the group receiving the **extracts** had improved lung function. After six weeks:[7]

- Total air exhaled (measured by a spirometry test, which measures lung capacity, how much air you can breathe into or out of your lungs) increased by **30%**,
- Forced air exhalation in one second (a measure of how well air flows through the airways) improved by **16.4%**, and
- Aerobic exercise capacity increased by **7.4%**.

In another study, subjects with mild to moderate **asthma** received either **200 mg** of **Boswellia-bael fruit** blend or a placebo.[18] Those receiving the extracts had a:

- **50%** improvement in peak expiratory air flow rate, which is usually reduced in asthma sufferers, and
- **44%** decrease in the use of an asthma rescue inhaler.

Researchers attributed these improvements to the **anti-inflammatory** activity of the extracts.

Saffron

Saffron is a spice that has long been used in traditional medicine for respiratory ailments.[19]

Preclinical studies show that saffron improves **lung function** through anti-inflammatory effects in the lungs[20] *and* by relaxing smooth muscles in the airways, improving airflow.[20-26]

In a human trial, patients with mild to moderate **asthma** received either **100 mg** of **saffron extract** daily or a placebo.[19,27]

After eight weeks, those in the saffron group had:

- **50%** less waking at night due to asthma symptoms,
- Fewer instances of shortness of breath during the night,
- Less limitation of physical activity,
- A **40%** reduction in use of an asthma rescue inhaler,
- Improvement in airflow in respiratory testing, and
- Reduction in markers of inflammation.

Andrographolide

Andrographolide is a compound extracted from the herb *Andrographis paniculata*. It has been used in eastern medicine for an array of health concerns.[28]

Cell and animal studies show that andrographolide can **shield the lungs** against damage caused by smoke and other pollution.[29-34]

It does so in several ways, including by:

- Protecting against **inflammation**,
- Defending against **oxidative stress**, and
- Preventing **DNA damage**.

By protecting the lungs and improving lung function, a combination of Boswellia-bael fruit, saffron, and andrographolide may help counter the damage that aging and poor air quality do to the respiratory system.

WHAT YOU NEED TO KNOW

Improve Lung Function

- Lung function generally deteriorates with age. Exposure to wildfire smoke, air pollution, and other toxins accelerates lung damage and is associated with increased risk for asthma, lung infections, and lung cancer.
- In a clinical study, a blend of extracts of *Boswellia serrata* resin and **bael fruit** was shown to improve lung function in healthy adults and asthma sufferers and to increase a measure of lung capacity by **30%**.
- **Saffron** has also been found to boost lung function and improve the clinical control of asthma, reducing use of a rescue inhaler by **40%**.
- The plant-derived compound **andrographolide** protects the lungs from damage due to poor air quality in cell and animal studies.
- Together, these ingredients may improve lung function and help shield the respiratory system from damage due to age and poor air quality.

Summary

Lung function tends to decline with age.

Exposure to wildfire smoke and other forms of pollution further accelerates lung damage and correlates with higher rates of lung disease, including **asthma** and **lung cancer**.

Clinical studies have found that extracts of *Boswellia serrata* and **bael fruit**, and **saffron,** improve lung function in a variety of ways and reduce symptoms of lung disease.

In preclinical studies, **andrographolide** has been shown to help defend lung tissue against the effects of pollution. •

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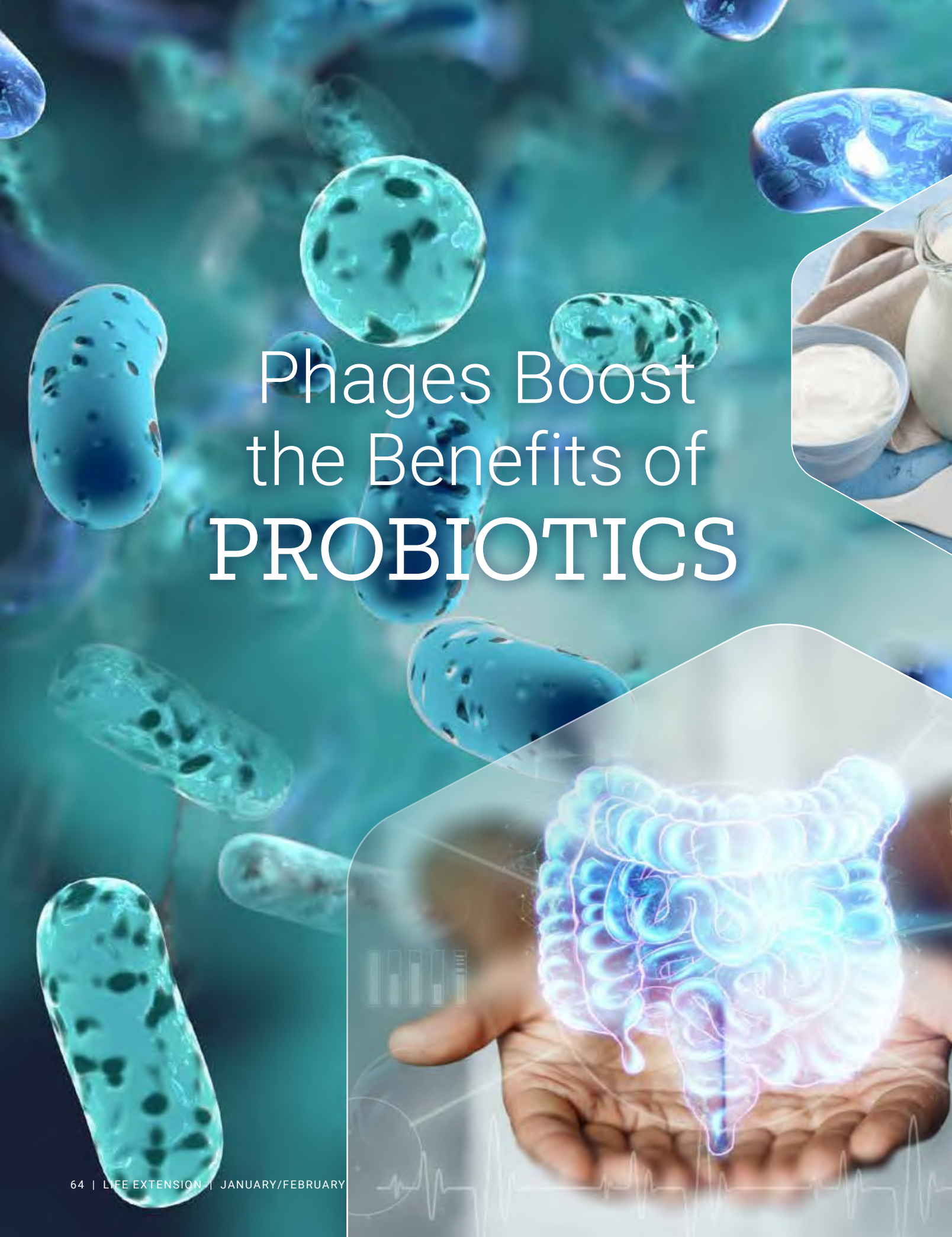

Phages Boost the Benefits of PROBIOTICS

BY PATRICIA WEISER, PHARMD

The impact of the **gut microbiome** influences our entire body.

Imbalances in microbiome composition have been linked to a host of common disorders including **inflammation**, autoimmunity, metabolic conditions, brain chemistry, and more.[1-3]

The good news is that the balance of the gut microbiome can be shifted towards one associated with ***better health***.[4-6]

One way to do this employs the combined use of probiotics and bacteriophages or "phages."

Phages are tiny packages of DNA or RNA wrapped in protein.

Each type of phage naturally attacks *only specific* types of bacteria.[7-9] By selecting specific phages, it is possible to target specific, potentially harmful bacteria in the digestive tract.

This allows a dual-approach strategy of using **probiotics** for their beneficial effects, while reducing competition from bacteria, of which we want less.

How Gut Health Impacts Overall Health

Gut bacteria affect almost *all* aspects of human health.

Researchers have estimated that a healthy adult individual's intestines host about **160** distinct bacterial species.[5] The presence or absence of certain species can have dramatic consequences.[10,11]

An enormous range of gut bacteria is necessary for optimal health. One important health-promoting property of some bacteria in the gut is the ability to produce **short-chain fatty acids**, compounds that have shown anti-inflammatory, immune-supportive, and neuroprotective activity, among other benefits.[12]

Certain factors, including advancing age,[13] poor diet,[13] stress,[13] antibiotic use,[13] and lack of physical activity,[10] can cause our microbiomes to become **imbalanced**, a state known as **dysbiosis**.[14]

This imbalance is associated with worse health.[4] Scientists have linked dysbiosis to colon infections, antibiotic-associated diarrhea, irritable bowel syndrome, autoimmune disease, allergic conditions, and obesity.[15,16]

Other harmful microbes in the gut can cause infections, inflammation, and gastrointestinal discomfort, and appear to contribute to the risk for chronic disease.[13,17]

Even in otherwise healthy individuals, a gut bacteria imbalance can trigger the development of digestive symptoms like **diarrhea**, **gas**, **bloating**, and **abdominal pain**.[18]

Gut bacteria even appear to play a role in the metabolism of **neurotransmitters** such as serotonin, a mood-regulating hormone.[19] That could help explain why people with certain gastrointestinal disorders have a higher risk of mental health conditions like **depression** and **anxiety**.[1,20]

Shifting the gut microbiota toward a healthy balance can ease digestive issues and improve overall health.

The Benefits of Probiotics and Phages

Research has established the many and varied benefits of taking oral probiotics. ***Lactobacillus*** and ***Bifidobacterium***, two of the most common probiotics, help ease symptoms of certain gastrointestinal diseases.[21]

Bacteriophages are lesser-known tools that help promote **gut** and **overall health**.[22]

The term "bacteriophage" literally means "**bacteria eater**." Phages are **selective killers**, only targeting and destroying specific bacteria.[7,9,23]

The phages can allow *beneficial* bacteria to flourish and grow at a greater rate by removing competing harmful species.[24]

Phages were discovered almost a century ago and were recognized by the FDA as early as 1958 as safe to use to help protect foods against the growth of undesirable bacteria.[25] Because they exclusively target bacteria and not animals or humans, and as suggested by their safety to use in the food supply, phages pose no health threat to humans.

However, research into phages as therapeutic agents in human infections fell out of favor with the discovery of antibiotics.[26] Today, as the threat of **antibiotic-resistant infections** and superbugs has become more concerning, medical research is refocusing on the potential of **phage therapy**.

Phages have now been used in numerous human trials and therapeutic settings with **no reports of adverse effects.**[27-32]

Combining probiotics with phages holds great promise for gut health and other areas impacted by the gut microbiome.

Human Trials

Researchers developed a targeted **four-phage blend** that can help rapidly decrease intestinal populations of the *unfavorable* bacteria ***E. coli***, while boosting growth of beneficial bacteria.[33,34]

In a **clinical study**, scientists tested the impact of these bacteriophages on the gut microbiome and gastrointestinal inflammation. Healthy adults received either the **four-phage blend** *(LH01-Myoviridae, LL5-Siphoviridae, T4D-Myoviridae, and LL12-Myoviridae)* or a **placebo** daily for 28 days.[34]

Compared to placebo, the **phage** blend was associated with:[34]

- *Increases* in **beneficial bacteria** in the gut,
- *Decreases* in *Escherichia coli* (***E. coli)*** bacteria, a common cause of diarrhea and other digestive problems, and
- *Decreases* in interleukin-4, a marker of **inflammation**.

This shows that phages can beneficially modify gut bacteria.

In another clinical study, researchers tested whether adding the **four-phage blend** to a common probiotic bacterium, ***Bifidobacterium lactis***, could enhance the effects of the probiotic.[33]

Healthy adults received either *B. lactis* or that probiotic with the four-phage blend for four weeks. Compared to the probiotic-only group, the group that consumed ***B. lactis*** plus the **phage blend** had:[33]

- Improvement in symptoms of **gastrointestinal inflammation**,
- Reduction in **colon pain**,
- A six-fold increase in beneficial ***Lactobacillus*** bacteria, and
- Decreases in the gastrointestinal tract in the amount of *Citrobacter and Desulfovibrio*, and a trend toward a decrease of *E. coli*, intestinal bacteria associated with inflammation, gastrointestinal dysfunction, infections, and other potentially serious health problems.

These observations suggest adding **phages** to **probiotics** could support probiotic benefits and aid in the shift toward a more favorable gut microbiome.

Improve the Microbiome with a Phage-Probiotic Blend

- The mix of microbes in our gut has a huge impact on digestive and overall health.
- Taking beneficial bacteria called **probiotics** can improve the balance of the gut microbiome.
- Bacteriophages, called **phages** for short, are packages of DNA or RNA wrapped in protein. They can selectively kill harmful bacteria, allowing probiotic bacteria to flourish.
- Combining phages with probiotics may boost the beneficial impact of the probiotic.

Summary

An unhealthy imbalance of bacteria in the gut can negatively affect gut and overall health.

Probiotics taken as supplements have helped balance intestinal flora.

Taking an oral combination of **probiotics** and **bacteriophages** may improve the health of the gut microbiome.

Phages show promise in relieving the functional changes caused by gut microbiome imbalance. This may be especially valuable for aging individuals. •

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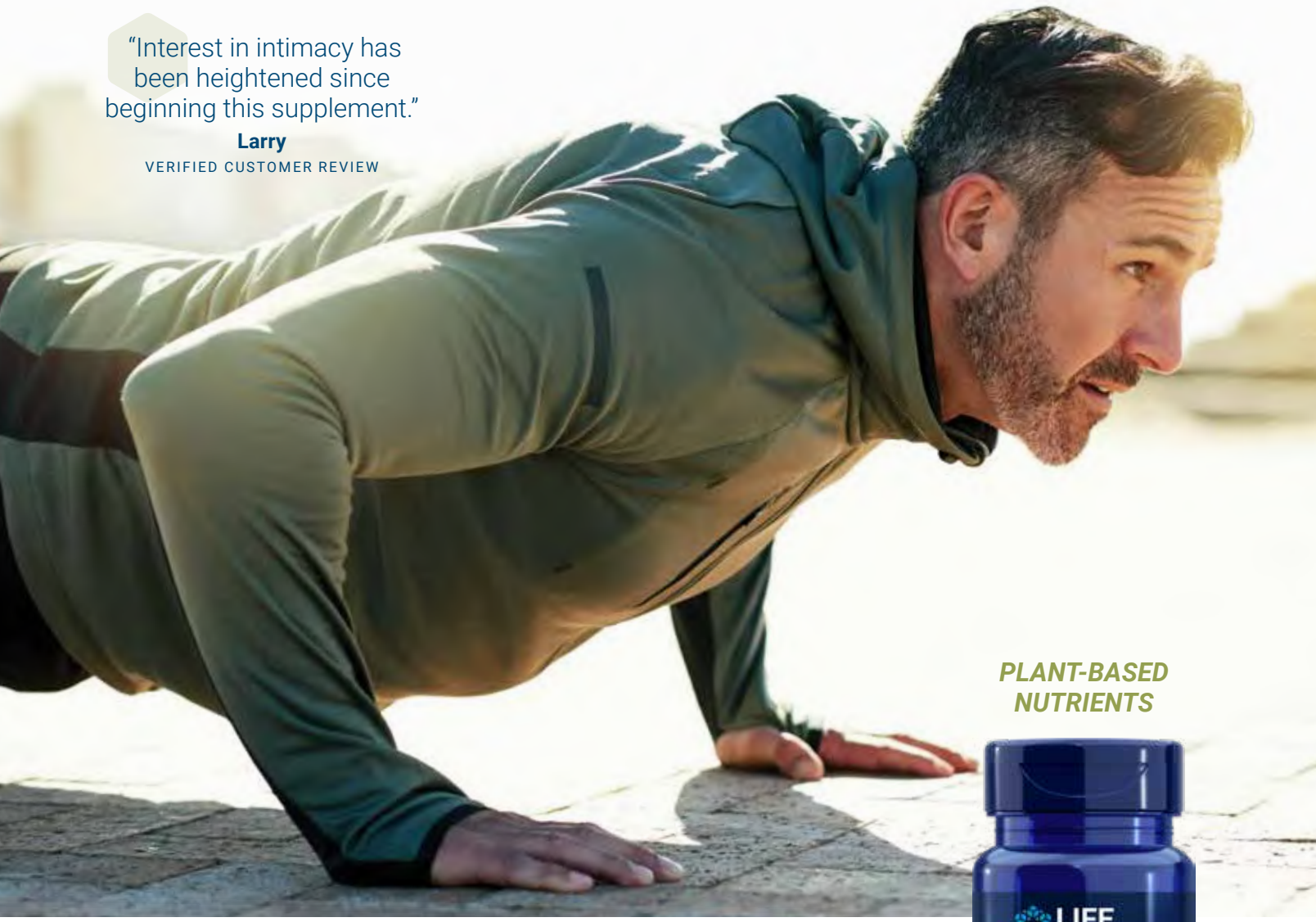

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Saffron

How PROBIOTICS Can *Reduce* Anxiety and Depression

BY HEATHER L. MAKAR

Roughly **25%** of adults in the U.S. suffer from **anxiety**, **depression**, or both.[1]

Many find that antidepressant drugs don't work for them, or they discontinue them as a result of side effects.

There's an alternative solution.

A link has been found between **gut health** and **mood disorders**.[2-5]

One trial in healthy **human** volunteers found that a blend of two **probiotics** improved median self-rated scores of feelings of **depression** and anxiety by **50%**—without side effects or dependence.[6]

Another **clinical trial** showed how a plant extract enabled antidepressive benefits without side effects.[7]

These ingredients may provide a safe way to **improve mood**.

Depression and Anxiety

Depression affects more than **21 million** adults in the U.S.[8] Rates of **anxiety** and **depression** skyrocketed during the pandemic.[9]

Medication and counseling can help. But **two thirds** of those taking antidepressants experience side effects,[10] including sexual dysfunction, fatigue, weight gain, and insomnia.[11]

Only a small percentage of people taking antidepressants get a clinically significant response. Because of this, many stop taking them.[12]

Roughly **60%** of those affected by mood disorders are not receiving treatment.[13]

The Gut-Brain Axis

Probiotics have been shown to provide some relief for symptoms of depression, and perhaps to a lesser extent symptoms of anxiety, in multiple clinical trials.[14,15]

The likely reason: the **gut-brain axis**.

Though we think of **neurons** primarily as brain cells, a network of **200-600 million** neurons lines the **gastrointestinal** tract.[16,20]

The **gut-brain axis** is a two-way communication system between the **digestive system** and the **brain**.[16-19]

The **gut microbiota** is the name for the trillions of bacteria and other microorganisms that live in our digestive tract. The greatest amounts are in the large intestine.

Some of these bacteria alter the synthesis and degradation of **neurotransmitters** that neurons in the gut use to transmit signals to regions of the brain responsible for mood regulation and learning.[5,21,22]

Stress and depression may alter gut bacteria and promote secretion of pro-inflammatory cytokines.[23] These signaling molecules can promote **inflammation** in the brain, which can *worsen* symptoms of mood disorders[23,24] and cognition.[24,25] Some of these bacteria may even encourage dysregulated eating.[26]

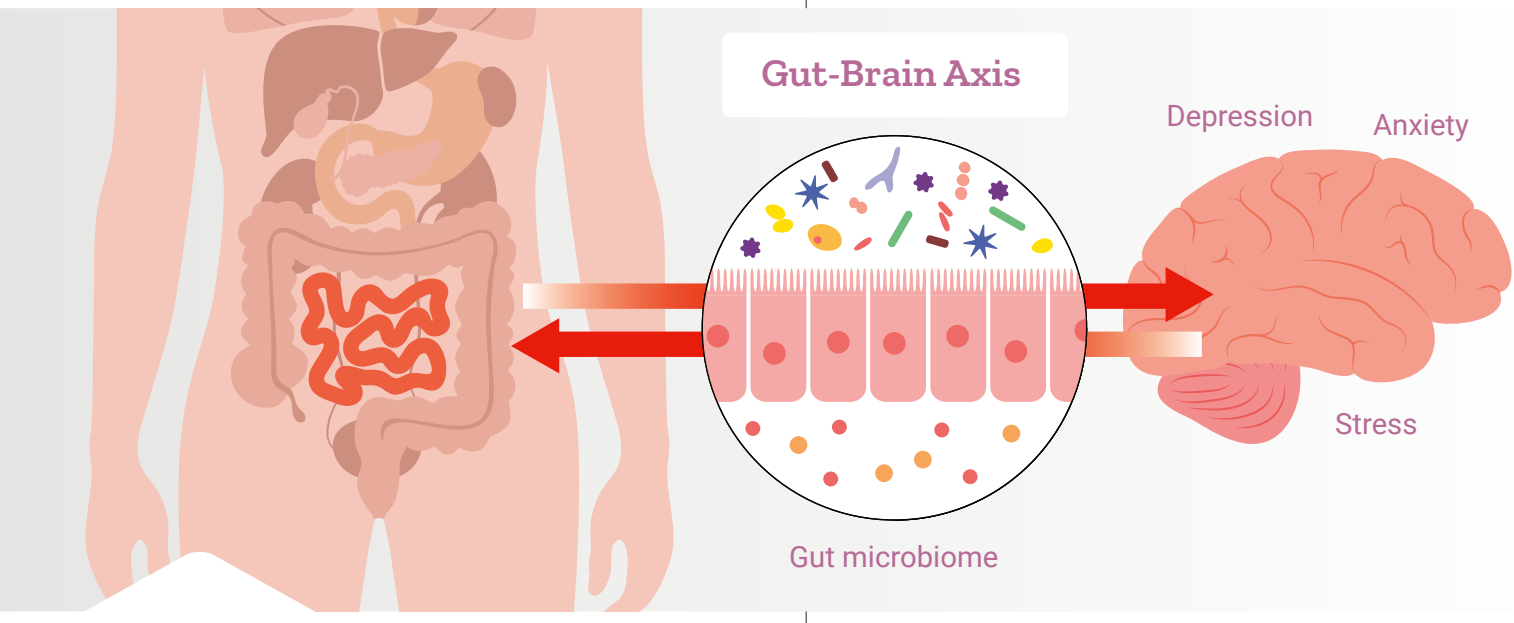
Probiotics Improve Mental Health

Probiotics are beneficial bacteria that support immune, digestive, and oral health. They also play a vital role in **psychological wellbeing**.[6,16,17,27]

The gut contains trillions of bacteria[21] with the neural system of the intestine composed of **200-600 million** neurons, cells that receive, process, and transmit information.[20]

The gut communicates with the brain through these neurons and the vagus nerve or by modulation of neuroactive compounds produced by the microbiome.[21]

- Gut microorganisms can produce/modulate via secretion of precursors, many kinds of **neurotransmitters** (chemicals that send signals from one neuron to another). They include precursors to **dopamine, serotonin,** and **norepinephrine**, which are important to regulating mood.[21]



- Probiotics have been shown, in a study in healthy individuals, to reduce self-rated scores for depression, anxiety, and stress.[28] Another study showed that treatment with ***Lactobacillus*** species resulted in lower levels of cortisol, an important stress hormone.[27]
- Preclinical evidence has shown that certain intestinal bacteria increase brain levels of **BDNF** (**brain-derived neurotrophic factor**), a growth factor known to promote neuron development, survival, and function, and support synapse health.[23]
- Stress is one of the factors that plays an integral role in **intestinal barrier function**, causing "leaky gut" which allows pro-inflammatory molecules to enter the blood, causing dysregulation of the immune system.[26] Chronic stress can also change the composition of the microbiome and impact its barrier function.[24] That, in turn, can negatively affect mood.[26]

Specific Probiotic Strains

Two strains of probiotic bacteria, ***Lactobacillus helveticus*** **R0052** and ***Bifidobacterium longum*** **R0175**, have been shown in animal models to play a role in beneficially modulating the **gut-brain** axis[6,27,29] by:

- Maintaining a **balance** of the **microbiome** by competitive exclusion of bad gut bacteria (such as clostridium).[27] Clostridium bacteria, for example are known to produce propionic acid that has been associated in other animal studies with anxiety and aggression,[30]
- Increasing levels of **doublecortin** (a protein that helps movement and differentiation of neurons) in the **hippocampus** (the brain's memory-processing region). Doublecortin is also a marker for new brain-cell formation in an experimental model of chronic stress. This increase may indicate that the brain is regenerating healthy tissue that can lead to future resilience against stress,[29]
- Supporting the hypothalamic-pituitary-adrenal axis balance,
- Reducing levels of **pro-inflammatory cytokines** and improving production of **anti-inflammatory** cytokines,[27] and
- Tightening the "leaky gut" induced by stress.[29,31]

WHAT YOU NEED TO KNOW

Improve Mood Without Side Effects

- Millions of Americans suffer from **anxiety** and **depression**, but many find prescription antidepressants ineffective, or they don't like the side effects.
- Two strains of probiotics, *Lactobacillus helveticus* **R0052** and *Bifidobacterium longum* **R0175**, stimulate beneficial neuromodulators that travel from the gut to the brain. In a clinical study, they reduced depression and anxiety scores by **50%** in healthy individuals.
- The spice **saffron** interacts with neurotransmitters in the brain. In clinical studies, it was as effective as multiple antidepressant and anti-anxiety drugs, including Prozac® and Celexa®.
- A combination of saffron and probiotics can work to relieve depression and anxiety and improve mood, without side effects.

Success in Human Trials

Human trials of these probiotics have shown impressive results in reducing symptoms of depression and anxiety.

In one clinical trial, healthy participants took either **three billion CFUs** (colony forming units) of combined ***Lactobacillus helveticus* R0052** and ***Bifidobacterium longum* R0175** or a **placebo** daily.

After one month, compared to **placebo**, those who took the **probiotics** had a:[27]

- **50%** improvement in **depression** scores,
- **49%** improvement in global severity index, a measure of overall **psychological distress**,
- **60%** improvement in **anger-hostility** scores, and
- **13%** reduction in free urinary cortisol, a measure of chronic **stress**.

A follow-up analysis of this study found that the **probiotic formula** also worked well in improving self-rated anxiety and depression scores in patients who began the study with low stress levels as measured by urinary cortisol. [6] As is the case with most probiotics, these were well tolerated with few, if any, side effects.

Anxiety and stress are associated with intestinal disturbances.[2]

In another trial, participants aged 18-60, with at least two self-reported symptoms of stress, were given either a placebo or the probiotic combination at the same dosage as in the other studies.[32]

After three weeks the probiotic-treated subjects experienced a **complete elimination** of stress-induced nausea and vomiting and, compared to the **placebo** group, approximately **8.6 times** the reduction in stress-induced abdominal pain, and **nearly double** the reduction in flatulence and gas.

Once again, the probiotics were found to be safe and did not cause unpleasant side effects.

Saffron Enhances Mood

Saffron has been used in Persian and Chinese medicine to treat depression for centuries.[33-35]

Preclinical research suggests it may help relieve depression and anxiety as a result of its potential influence on three **neurotransmitter-**signaling pathways involved in mood regulation in the brain:

- **Dopamine**,[36] which contributes to feelings of pleasure, learning, and motivation,[37]
- **Serotonin**,[38] responsible for a behavior pattern, mood, sleep pattern, anxiety, feelings of comfort, and well-being, and[37]
- **Norepinephrine**,[39] responsible for alertness, arousal, decision-making, focus, and attention.[37]

Effective in Clinical Trials

In a series of human studies, researchers tested **30 mg** of **saffron** head-to-head against common antidepressant drugs, including:

- Imipramine (Tofranil®),[40]
- Fluoxetine (Prozac®),[33,41] and
- Citalopram (Celexa®).[42]

In each case, **saffron** was found to be as effective as the drug in treating depression.

Combining the probiotics ***Lactobacillus helveticus* R0052** and ***Bifidobacterium longum* R0175** with an extract of **saffron** offers a multipronged attack on **anxiety** and **depression** and a way to boost mood without side effects.

Summary

The probiotics ***Lactobacillus helveticus* R0052** and ***Bifidobacterium longum* R0175** work through the gut-brain axis to reduce feelings of depression and anxiety.

Saffron extract interacts with neurotransmitters to improve mood and has been shown to work as well as prescription drugs to treat depression.[7,43]

A combination of these ingredients is not associated with significant side effects and could help people struggling with anxiety and depression. •

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PQQ and Diabetic Kidney Disease

BY LAWRENCE HARDING

An astonishing **37.3 million** Americans have **diabetes**[1] (type II accounts for **90%-95%** of the cases).[2]

That's more than **11%** of the population.[1]

The prevalence of **diabetes** and **metabolic syndrome** is *increasing* in the U.S.[3,4]

The **kidneys** are particularly susceptible to the damage caused by high blood sugar.[5]

Recent estimates find that nearly **50%** of people with type II diabetes will eventually suffer from **kidney disease**.[6] Alarmingly, as diabetes rates skyrocket, so does the incidence of diabetic kidney disease.[7]

Pyrroloquinoline quinone (**PQQ**) has been shown in lab and animal studies to ***protect the kidneys*** and other tissues from the harmful effects of poor blood glucose control.[5,8-11]

Diabetes and Kidney Disease

When people suffer from metabolic diseases like **diabetes**, chronically high levels of blood sugar can cause widespread damage to most tissues of the body.

Over time, this can lead to risk for multiple long-term complications including cardiovascular disorders, vision loss, neurovascular insufficiency, and kidney failure.[12]

The **kidneys** are especially susceptible to damage in diabetics. Over time, kidney function deteriorates and can lead to **kidney failure**. At that point, an individual will require dialysis or a kidney transplant to survive.[13]

Long before kidney failure develops, people with metabolic disease should do everything possible to protect their kidneys from damage.

PQQ Improves Mitochondrial Function

Pyrroloquinoline quinone (PQQ) is a compound produced by many bacteria found in soil.

PQQ is absorbed by plants and is found in fruits and vegetables.[14] It is a vitamin-like compound that has demonstrated impressive biological effects.[15,16]

One of PQQ's key functions is to support the **mitochondria**, the energy powerhouses found in all cells. It supports optimal mitochondrial function.[9,17]

As we age, the body experiences a decline in mitochondrial activity and resilience.[18]

PQQ has been shown to ***improve mitochondrial function*** and stimulate the creation of ***new mitochondria***.[19-21] This may help rejuvenate cellular function and counter metabolic disorders like type II diabetes.[22,23]

In addition to its impact on mitochondria, PQQ inhibits a protein known as **PTP1B**, which is associated with **insulin resistance**.[24]

Insulin is the hormone that helps cells take up and use glucose. Inhibiting PTP1B improves **insulin sensitivity** in diabetic mice, making cells more responsive to insulin. That *reduces* high blood glucose levels.

In rodent models of **diabetes**, several metabolic problems are normally seen. In addition to high blood glucose, there are elevated levels of cholesterol and triglycerides and reduced levels of antioxidants in tissues.[10]

Giving these animals **PQQ** *reverses* these problems—lowering glucose, cholesterol, and triglycerides while boosting antioxidant protection in tissues, including in the kidneys.[5,10,11,19,24,25]

Protecting Against Kidney Damage

Kidney disease is one of the most common complications of diabetes. Researchers are constantly searching for ways to defend kidney function and avoid progression to **kidney failure**.

The results of studies in animal models indicate that **PQQ** use helps protect the kidneys, even in the face of diabetes and elevated blood glucose levels.[5,10,11]

In rodent models of diabetes, the kidneys show signs of significant damage and develop **fibrosis** (scarring). Kidney function is decreased and there are signs of oxidative stress and inflammation in the tissues.[5]

Treating the animals with PQQ *reversed* these changes, **improving kidney function** and **decreasing damage** to the kidneys.

PQQ is believed to accomplish this by enhancing mitochondrial function and relieving oxidative stress.[14]

Taking **10 mg** to **20 mg** of PQQ daily is often recommended as part of any anti-aging program, and may benefit anyone with elevated blood sugar, diabetes, or other metabolic disease.

Summary

Diabetes and its complications affect millions of people and damage tissues throughout the body. A particularly high number of people with diabetes suffer from **kidney disease**.

Studies in animal models have found that the compound **pyrroloquinoline quinone (PQQ)** can *reverse* many of the metabolic problems associated with type II diabetes and **shield kidneys** from the harmful impact of high blood sugar.

It is believed that these beneficial effects result from PQQ's ability to boost mitochondrial function and relieve oxidative stress.

Diabetic animals receiving PQQ have significant improvements to their metabolism and are protected from the kidney damage normally observed in diabetes.

Human studies are urgently needed to assess whether these effects seen in laboratory models translate into improved clinical outcomes. •

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Deliver More QUERCETIN to Cells

BY RICHARD SANTOS

Quercetin has become a popular supplement for good reason.

Studies show that **quercetin**, a plant **flavonoid** functions in several ways, including:[1-5]

- Promoting better cardiovascular health,
- Protecting cognitive function,
- Improving metabolic health, and
- Helping rid the body of dysfunctional senescent cells.

Standard or unformulated quercetin has relatively low **bioavailability**. That means that little of it gets into the blood and cells following consumption.

In recent years, scientists have developed various ways to improve quercetin's **bioavailability**.

In a new development, scientists have created an innovative method to further *increase* quercetin's bioavailability.

In a **human** study, a novel quercetin compound was shown to *boost* total **bioavailability** up to ***62 times*** compared to unformulated quercetin.[6]

This new formulation also delivered ***18 times*** more *bioactive* **free quercetin** than unformulated quercetin.[6]

A Better Quercetin

For many people, there's an obstacle to getting the full benefits of quercetin: Standard quercetin suffers from poor **bioavailability**.

Much of what is consumed never makes it into the bloodstream and to cells where it could help.

A randomized placebo-controlled study found that **bioavailability** of quercetin has reached new heights.

This quercetin is first encapsulated in plant-derived particles called **micelles**.

These micelles are then combined with a **hydrogel** made from a non-digestible fiber found in fenugreek seeds called **galactomannans**. This fiber hydrogel acts as a scaffold for the micelles, protecting them and the **quercetin** within.

This formulation significantly ***improves*** the ***bioavailability*** of quercetin.

In a **clinical trial**, healthy adults received either unformulated quercetin or the new galactomannan hydrogel formulation. With the new formula, the bioavailability of quercetin was found to be up to ***62 times greater*** compared to the unformulated.[6]

In addition, the peak concentration of quercetin in the blood was greater and the **half-life** more than **doubled**. This means that more quercetin makes it into the bloodstream *and* stays there longer, giving it time to be absorbed into tissues and cells where it can exert its benefits.

The hydrogel quercetin not only increases the **total quercetin** absorbed, but it increases the amount of **free quercetin** in the blood as well.

Importance of Free Quercetin

When quercetin is absorbed into the body, much of it is chemically bound to other compounds (conjugated).

Conjugated forms of quercetin have some health benefits, but increasing **free quercetin**, which is unbound to other compounds, may offer additional benefits.

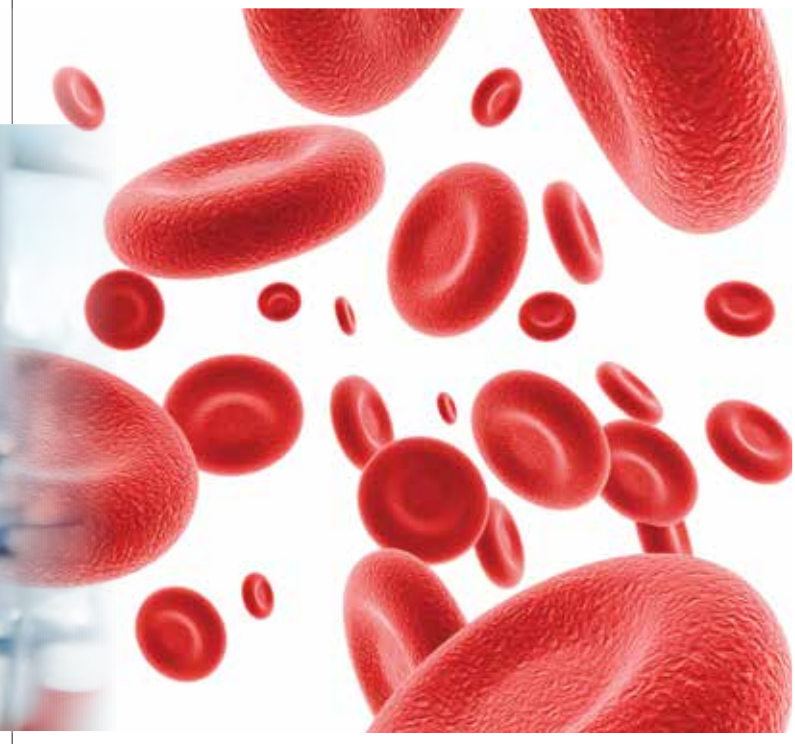
This has been shown in animal studies. In one, scientists gave quercetin to two groups of rats with high blood pressure.[7] Through experimental manipulation, they were able to ensure that one group had more **free quercetin** than the other.

The group *without* free quercetin had no significant change in blood pressure, while the group with more **free quercetin** had a nearly **30%** drop in average blood pressure.

This suggests that the presence of **free quercetin** in the body may be essential for certain health benefits. This may be due to free quercetin's ability to cross membranes into cells more readily than bound forms.

Unformulated quercetin yields relatively low levels of free quercetin in the blood, potentially limiting its benefits.[6]

This **hydrogel** form of quercetin changes all that. It is the first formulation to demonstrate significantly *higher* blood levels of **free quercetin**, leading to amounts approximately ***18 times higher*** compared to unformulated quercetin.[6]



WHAT YOU NEED TO KNOW

Benefits of Quercetin

Flavonoids are compounds found in many fruits, vegetables, and herbs.

A diet high in **flavonoids** is associated with better health, lower risk for many age-related chronic conditions, and reduced rates of death.[8-13]

Quercetin is one of the most abundant flavonoids found in plant-based foods, including onions, kale, broccoli, and apples.[1-5]

Hundreds of cell, animal, and human studies of **quercetin** have shown a range of effects, including:[1-5]

- Anti-inflammatory action,
- Anti-microbial activity against bacteria, fungi, and viruses,
- Anti-cancer properties,
- Anti-diabetic effects,
- Metabolic improvements including reduced blood pressure, anti-obesity effects, and improved blood lipids,
- Protection of blood vessel health, including anti-atherosclerosis activity,
- Neuroprotective actions, including protecting the brain from cognitive decline and neurodegenerative disorders such as Alzheimer's disease, and
- Protecting the heart and reducing risk for cardiovascular disease.

Maximizing the Benefits of Quercetin

- **Quercetin** has been shown in many studies to have wide-ranging health benefits and life-extending potential.
- Unformulated quercetin suffers from poor **bioavailability**. Only small amounts make it into the bloodstream after consumption.
- Scientists have developed a new quercetin formulation that boosts bioavailability more dramatically than any previous forms.
- Protected in a hydrogel of fenugreek seed-derived fiber, quercetin is able to reach much higher blood levels and remain in the bloodstream for longer. This new form also increases levels of bioactive **free quercetin** more than unformulated quercetin.
- These changes may allow quercetin to reach its full potential at last.

Meta-analyses of human trials found that daily quercetin intake significantly decreased **systolic** (top number) and **diastolic blood pressure** in patients with metabolic disease and with high blood pressure.[14,15]

One meta-analysis of human trials also found that taking quercetin for at least eight weeks improved lipid profiles by increasing protective **HDL cholesterol** (the "good" cholesterol) and decreasing **triglycerides** in patients with metabolic disease or obesity.[14]

Another found that quercetin reduced total cholesterol, **LDL** ("bad") cholesterol, and **C-reactive protein** (a marker of systemic inflammation) in patients with metabolic disease.[16]

Many more clinical trials of quercetin for various conditions are currently underway. At the time of publication, a **National Institutes of Health** website (clinicaltrials.gov) lists 44 human trials of quercetin in the U.S. alone.

Summary

Many people take **quercetin** for its potential to improve health and extend life.

Unformulated forms of quercetin have poor **bioavailability**.

A novel formulation protects quercetin in the gut. This enables a major increase in the amount of absorbed **bioavailable quercetin** *and* the time it stays in the body.

In addition, this new formula increases blood levels of bioactive **free quercetin** beyond unformulated quercetin and previously available forms. •

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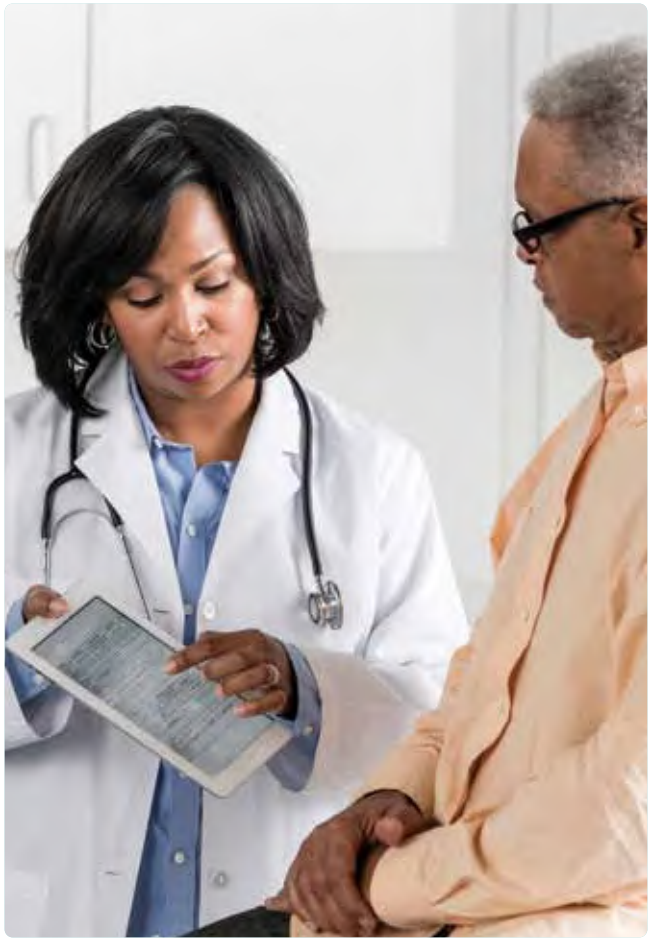

ZINC UP YOUR IMMUNE HEALTH

"It gives my immune system an extra kick when needed."

Tina

VERIFIED CUSTOMER REVIEW

Item #01813

50 mg • 90 vegetarian capsules

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GLUTEN FREE

Supplemental zinc can inhibit the absorption and availability of copper. If more than 50 mg of supplemental zinc is taken daily for more than four weeks, 2 mg of supplemental copper should also be taken to prevent copper deficiency.

You know zinc is good for you—but are you getting enough?

Zinc promotes critical **immune** functions and healthy **bones**.

This formula provides **50 mg** of zinc in a convenient, vegetarian capsule.

This product is available at fine health food stores everywhere.

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Restore Youthful Cellular Energy with PQQ

PQQ (*pyrroloquinoline quinone*) activates genes involved in the production of cellular energy.[1-5]

Studies show **PQQ** supports heart health and cognitive function, complementing CoQ10.[6,7]

In fact, just **20 mg** per day of **PQQ** plus **CoQ10** promotes memory and attention in aging individuals.[8]

This formulation contains **20 mg** of **PQQ** per capsule, which is the recommended daily dose.

This product is available at fine health food stores everywhere.

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30 vegetarian capsules

GLUTEN FREE · 1 DAILY · NON GMO LE CERTIFIED

Also available are **10 mg PQQ caps** (Item #01500) and **Super Ubiquinol CoQ10 with 10 mg PQQ** (Item #01733).

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Taurine has a range of potential anti-aging benefits, but levels in our body decline over time.

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1000 mg
90 vegetarian capsules

Item #00133

300 grams

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Introducing Life Extension® DOG

We've been passionate about health for over 40 years. We're now proud to offer soft chews for dogs, made with the same quality and attention to detail as all our supplements.

Multivitamin & Probiotics

Vitamins,[1] manganese,[2] colostrum,[3] turmeric,[1] and 6 probiotics[1,4,5] in this **chicken-flavored** soft chew supplement helps support a dog's overall health and diverse microbiome.

Item #02524
90 soft chews
Food Supplement

Stress & Behavior

L-theanine[1] and melatonin[1] in this **bacon-flavored** soft chew supplement helps promote calmness and relaxation so your dog can keep an even keel.

Item #02525
120 soft chews
Health Supplement

Hip & Joints

In human and animal studies PEA,[9] glucosamine,[1,10] and MSM[1] supplementation have been shown to promote healthy, comfortable joints. This **beef-flavored** soft chew supplement is just what your dog needs to keep moving comfortably.

Item #02523
90 soft chews
Health Supplement

Skin & Coat

This **salmon-flavored** soft chew supplement contains **omega-3**-rich fish oil for healthy coat and skin. This has been shown in clinical studies to help promote skin and coat health for dogs with sensitive skin[6] and to maintain a healthy coat.[6-8]

Item #02522
90 soft chews
Food Supplement

These products are available at fine health food stores everywhere.

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NEW PRODUCTS

Goodnight, Restless Nights.

Do you ever feel like you're not getting "enough sleep"? The number of hours you spend in dreamland may not be all that matters: when you sleep, your body goes through a restorative process.

If the various stages of sleep are interrupted, you may experience general fatigue as well as stress.

Our new Serene Sleep formula is a melatonin-free way to get the restful sleep you need. It uses ashwagandha and black cumin extracts to promote a healthy response to stress so you can put to bed any thoughts that were keeping you up at night.

Each extract has been clinically studied to encourage restorative sleep and stress relief to help ease you into the sleep of your dreams.

Get the restorative sleep you need, so you're ready to take on the day the next morning!

Item #02526 • 30 softgels

For occasional sleeplessness.

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

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