



The Science of a Healthier Life®

MARCH/APRIL 2021

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A woman with blonde hair, wearing a purple jacket and a black headband, is smiling and looking upwards in a snowy, mountainous landscape. She is wearing black gloves and has her arms raised slightly. The background is a bright, snowy mountain range under a clear sky.

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PLUS: Should You Try Intermittent Fasting?

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This product is available at fine health food stores everywhere.

References

1. *Appl Physiol Nutr Metab.* 2018 Apr;43(4):412-4.
2. *J Clin Psychiatry.* 2015 Mar;76(3):319-26.
3. *Eur J Nutr.* 2011 Aug;50(5):387-9.
4. *J Alzheimers Dis.* 2015;48(2):403-10.
5. *JAMA Psychiatry.* 2017 Oct 1;74(10):1005-10.



Item #02403

1000 mcg • 100 vegetarian capsules



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Reference

*Br J Pharmacol. 2004 Mar;141(5):825-30.

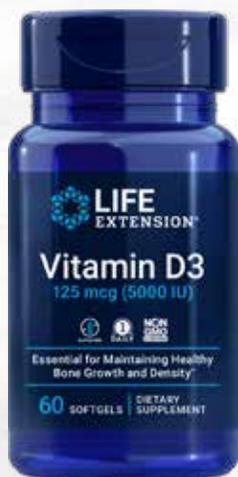
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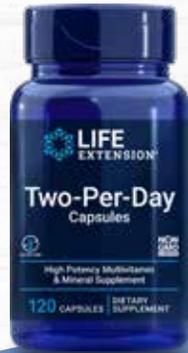
March/April 2021

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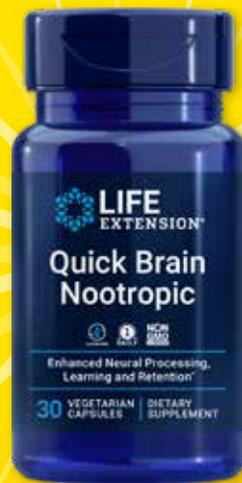
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In the News



Caloric Restriction Protects Against Liver Disease, Animal Study Suggests

Consuming fewer calories has a protective effect against developing hepatocellular carcinoma (primary liver cancer) associated with hepatitis C virus infection, and nonalcoholic fatty liver disease, according to a rodent study published in the journal *Liver Cancer*.*

The study used mice with the liver cancer core gene that spontaneously develop fatty liver and tumors. For 15 months, the animals were given either a control diet that allowed them to eat as much as they liked, or a diet that contained **30%** fewer calories than the control.

At the end of 15 months, animals that received calorie-restricted diets had fewer and smaller liver tumors, less liver oxidative stress, lower inflammation, downregulation of pro-cancer mediators, increased autophagy, as well as other improvements, compared to the control group.

Editor's Note: "Recently, worldwide increases in obesity and metabolic syndrome have raised the prevalence of primary liver cancer derived from nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), indicating a close relationship between over-nutrition and liver tumorigenesis," the authors stated.

* *Liver Cancer*. 2020 Sep;9(5):529-548.

Why Does Being Overweight or Obese Increase Alzheimer's Risk?

Numerous studies have shown that obesity increases the risk of Alzheimer's disease, but they haven't identified why the connection exists. A recent brain-imaging study published in the *Journal of Alzheimer's Disease* has identified an underlying connection.*

Researchers analyzed over 35,000 brain scans of more than 17,000 individuals, using SPECT (single-photon emission computerized tomography). They found that people with a *higher* body mass index had decreased blood flow to the brain. The subjects ranged in age from 18 to 94.

Decreased brain blood flow is the number one brain-imaging predictor of Alzheimer's disease.

As people progressed from overweight to obese to morbidly obese, reduced blood flow progressively worsened. In addition, the areas of the brain impacted by reduced blood flow were those especially vulnerable to Alzheimer's disease.

This is one of the largest brain imaging studies, until now, tying obesity to brain dysfunction.

"This study shows that being overweight or obese seriously impacts brain activity and increases the risk for Alzheimer's disease as well as many other psychiatric and cognitive conditions," said Dr. Daniel G. Amen, lead author of the study, and founder of Amen Clinics.

Editor's Note: "Overall, we have found a strong set of relationships between being overweight and obese and brain hypoperfusion across a large adult cohort spanning young adults to late life. The persistence of these abnormalities despite adjusting for demographic and psychiatric factors further highlights the need to address obesity as a target for interventions designed to improve brain function, be they AD prevention initiatives or attempts to optimize cognition in younger populations," the authors concluded.

**J Alzheimers Dis*. 2020;77(3):1331-1337.



Greater Cruciferous Vegetable Intake Associated with Less Aortic Calcification

Research findings reported in the *British Journal of Nutrition* reveal an association between increased intake of Brussels sprouts, broccoli, cabbage, and other cruciferous vegetables, and less extensive abdominal aortic calcification (AAC) in older women.*

Conducted by researchers from the University of Western Australia, the study included 684 women, with a mean age of 75, who had enrolled in the Calcium Intake Fracture Outcome Study in 1998. Responses to dietary questionnaires administered upon enrollment provided information about cruciferous vegetable intake. Aortic calcification was categorized as extensive or not extensive based on imaging obtained during 1998–1999.

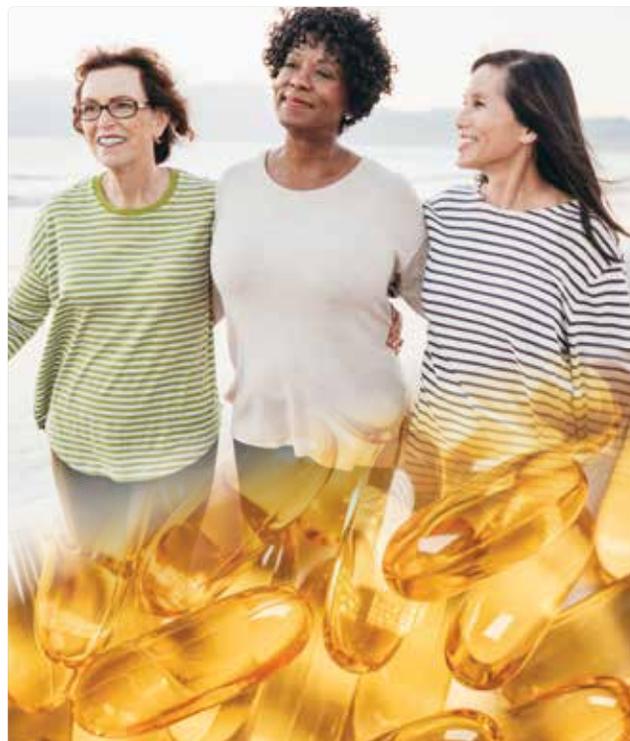
A correlation was observed between greater cruciferous vegetable intake and a reduction in AAC. Women whose intake of the vegetables was more than **44.6 grams** per day (the equivalent of ¼ cup of steamed broccoli or ½ cup of raw cabbage, for example) had a **46%** lower adjusted risk of extensive AAC, compared to those whose intake was less than **15 grams** daily.

Total vegetable intake, including other types of vegetables, was not related with risk.

“This study strengthens the hypothesis that higher intake of cruciferous vegetables may protect against vascular calcification,” the authors stated.

Editor’s Note: “One particular constituent found abundantly in cruciferous vegetables is vitamin K which may be involved in inhibiting the calcification process that occurs in our blood vessels,” said lead author Dr. Lauren Blekkenhorst.

* *Br J Nutr.* 2020 Jul 17.



Cardioprotective Benefits Found with Omega-3 Supplements

An updated meta-analysis published in *Mayo Clinic Proceedings* expands on an earlier one, supporting a cardioprotective role for supplementation with the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).*

This meta-analysis included 40 randomized controlled trials with a total of 135,267 participants.

Dosages of omega-3 used in the studies ranged from **400 mg** to **5,500 mg** per day.

Supplementation with EPA + DHA was associated with a:

- **13%** lower risk of heart attack,
- **10%** lower risk of coronary heart disease events,
- **35%** lower risk of fatal heart attack, and
- **9%** lower risk of coronary heart disease mortality.

Editor’s Note: When the impact of omega-3 dosage was examined, higher doses were more protective against the risk of cardiovascular disease events and heart attack than lower amounts.

* *Mayo Clin Proc.* 2020 Sep 17.

Glucosamine and Chondroitin Intake Linked to Lower Risk of Premature Mortality

Regular supplementation with glucosamine and chondroitin is associated with a lower risk of mortality, according to the results of a study published in the *Journal of the American Board of Family Medicine*.*

The study included 16,686 participants in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2010. Participant interviews ascertained the use of dietary supplements during the previous month. Individuals who reported using glucosamine and chondroitin for a year or more were identified as glucosamine/chondroitin users in the current investigation.

During a median follow-up period of 107 months, 3,366 deaths occurred, of which 674 were caused by cardiovascular disease. Regular use of glucosamine/chondroitin was associated with a **58% lower** adjusted risk of dying from cardiovascular disease and a **27% lower** risk of dying from any cause during follow-up.

Editor's Note: Glucosamine and chondroitin are nutrients that are often consumed in combination to support joint health. Many individuals use glucosamine and/or chondroitin supplements on a regular basis to help maintain healthy joints or relieve some of the symptoms of arthritis.

* *J Am Board Fam Med.* Nov-Dec 2020;33(6): 842-847.



Omega-3 Fatty Acids as Add-On Therapy for Periodontitis

A review and meta-analysis included six studies that involved the use of the omega-3 fatty acids **EPA** and **DHA** in the treatment of periodontitis.¹ In four of the six studies, clinical attachment level and probing depth revealed significant improvement in association with omega-3 supplementation, compared to a placebo.

A randomized trial evaluated the effects of omega-3 supplementation in participants with chronic, moderate periodontitis.² Clinical attachment level improved at both one and three months among participants who received omega-3 in comparison with the control group, and compared to the beginning of the study.

In another trial, patients with periodontitis received scaling and root planing, while some of the subjects also received EPA and DHA.³ The study documented improvement in clinical attachment loss, bleeding on probing, and probing depth in the group that received omega-3.

Editor's Note: These studies provide growing evidence that omega-3 supplementation could be a promising adjunct to standard periodontitis therapy. As the authors of the review and meta-analysis noted, an alternative to antibiotics used in periodontal therapy could help solve, in part, the potential problem of antibiotic resistance in this group of patients.

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Adults Over 45 with Healthy Diets are Less Prone to Depression

The intake of fruit, vegetables, and omega-3 fatty acids can help protect against the risk of depression in older adults, according to an article in *BMC Psychiatry*.*

The study included 27,162 men and women between the ages of 45 to 85 who participated in the Canadian Longitudinal Study on Aging. Demographic data, depression, physical health, dietary intake, and other factors were assessed upon enrollment.

For men, being in a relationship, having a high intake of omega-3 fatty acids, fruit and vegetables, calcium, and high vitamin D sources, as well as other factors, were protective against depression.

Among women, chronic pain, stage 1 hypertension, low intake of fruit and vegetables, and other factors were associated with a greater risk of depression.

Editor's Note: The authors note that fruit and vegetables contain magnesium, zinc, and selenium that may help reduce inflammation, which is associated with depression. Additionally, fruit and vegetables contain antioxidants that decrease the effects of oxidative stress on psychological health.

* *BMC Psychiatry*. 2019 Nov 6;19(1):329.



Ashwagandha Supplementation Associated with Improved Sleep, Alertness, Quality of Life

A randomized trial published in *Cureus* found improvement in sleep, alertness, and quality of life among older men and women treated with the herb ashwagandha.*

The trial included 50 men and women between the ages of 65 to 80. Half of the group received **ashwagandha root extract** twice daily and the remainder received a placebo for 12 weeks. Quality of life, daytime sleepiness, sleep quality, and mental alertness upon rising were evaluated at the beginning of the trial, at four and eight weeks, and at the end of the treatment period.

Quality of life, including global, physical, psychological, social, and environmental aspects, significantly improved from baseline levels among the group that received ashwagandha.

In comparison with the placebo, sleep quality and mental alertness improved in the ashwagandha-treated group.

Ashwagandha was well tolerated and reported as safe and beneficial by those who received it.

Editor's Note: Ashwagandha is one of the most important herbs used in Ayurveda. It has been found to increase testosterone levels and lower cortisol levels in humans, lengthen the life of roundworms, and increase the activity of telomerase, an enzyme that lengthens telomeres (protective genetic material that caps and protects the ends of chromosomes) in cell cultures.

* *Cureus*. 2020 Feb 23;12(2):e7083.



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1. *J Altern Complement Med.* 2018;24(1):37-47.
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Lab data suggest **spearmint polyphenols** may promote the growth of new **brain cells**.²

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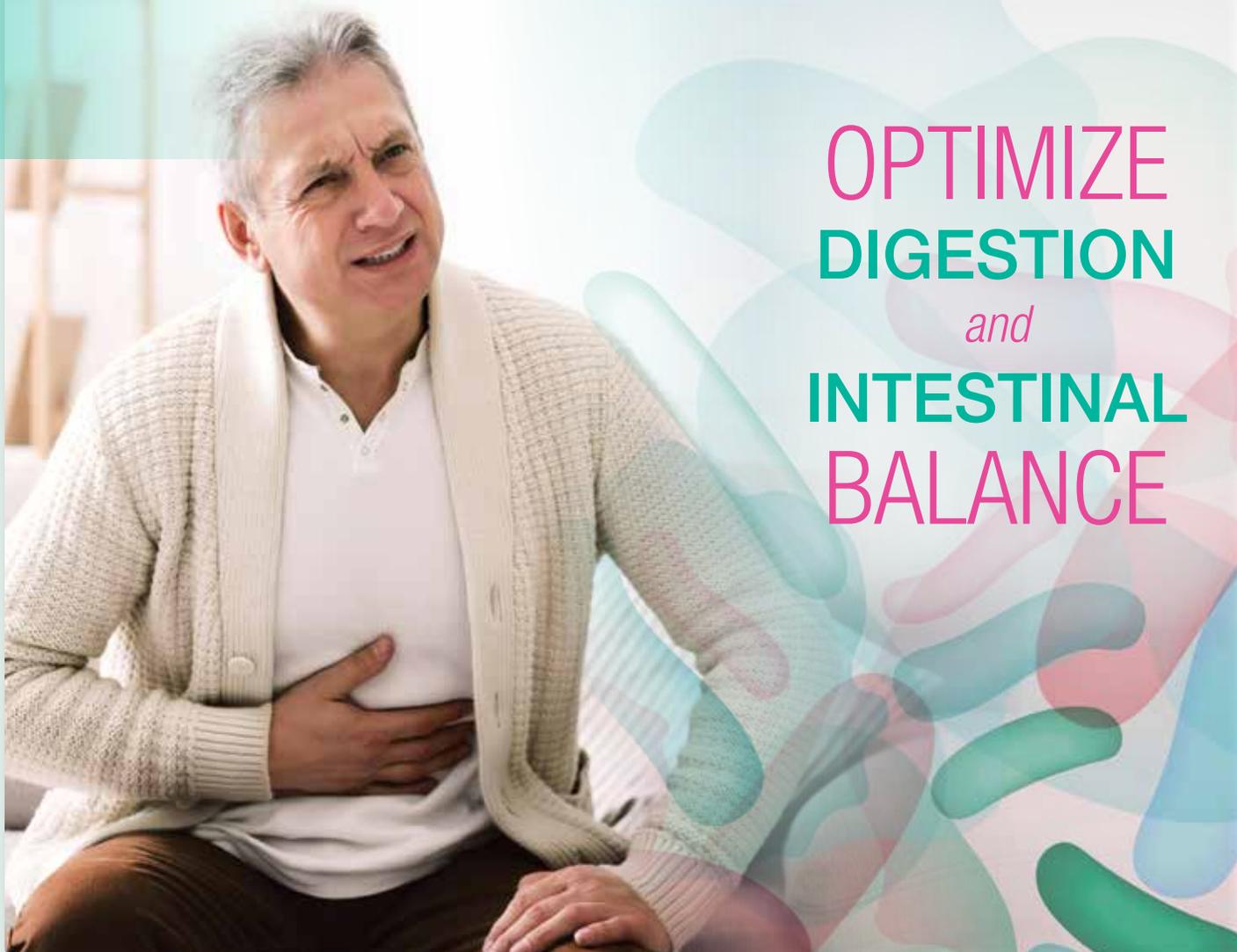


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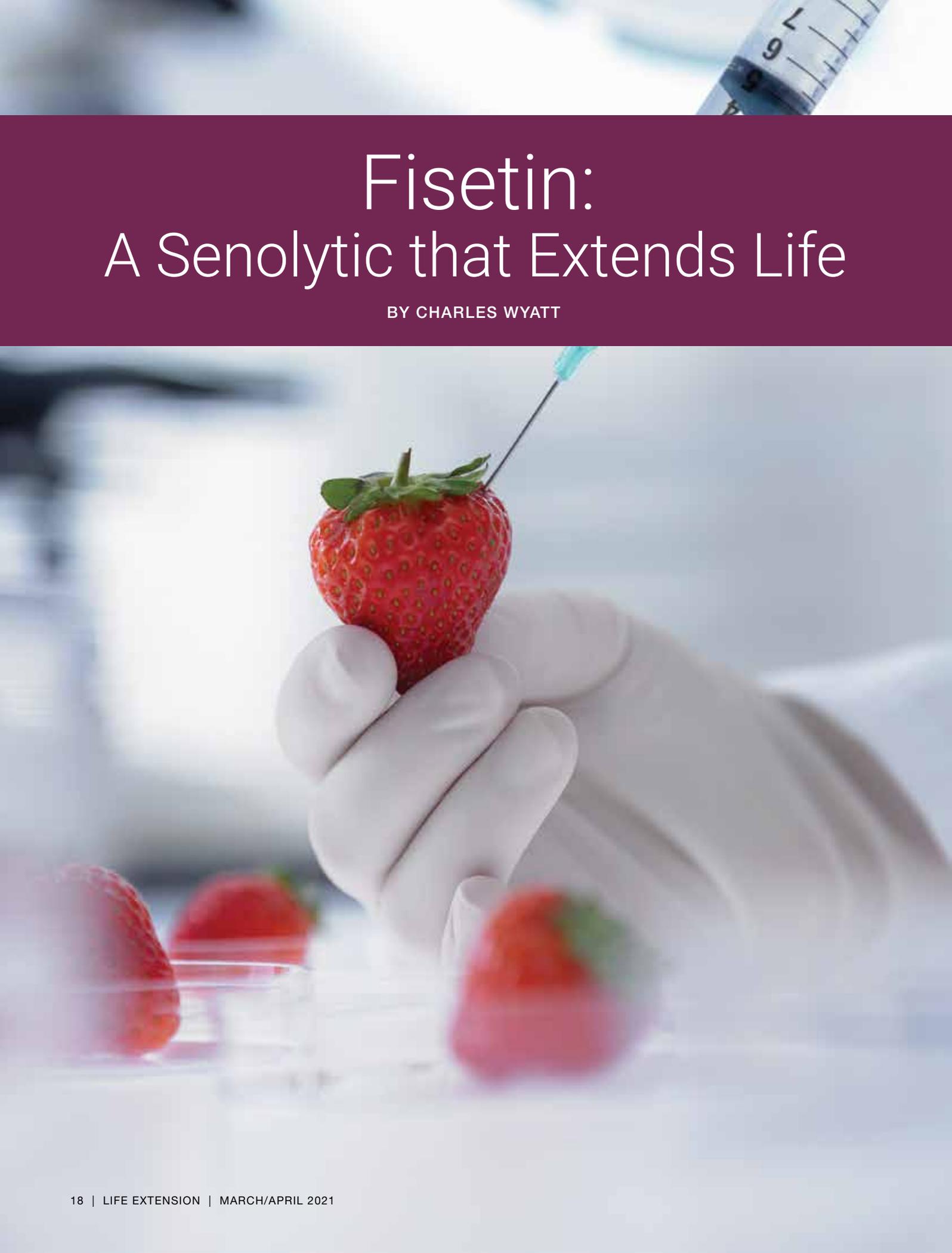
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Fisetin: A Senolytic that Extends Life

BY CHARLES WYATT

Senolytics have been shown to improve health and extend lifespan in experimental models.

These compounds work by helping the body clear away old, damaged (senescent) cells to make way for new, healthy cells.

Fisetin, a flavonoid found in various plants, is **one of the most powerful natural senolytics** ever discovered.

Preclinical and some preliminary clinical studies suggest it may protect against age-related disorders,¹⁻¹⁵ slow certain aging processes, and promote longevity.^{10,16}

Old mice given **fisetin** had a nearly **10% increase in lifespan**.¹⁷

One challenge has been that **fisetin** is rapidly metabolized in the digestive tract. This means very little is **absorbed** into the blood stream.

But scientists have developed a way to overcome this problem by combining it with natural compounds from the fenugreek plant.

This novel formulation increased the **bioavailability** of fisetin by as much as **25 times**.¹⁸



What Is Fisetin?

Fisetin is a flavonoid that has gained popularity in recent years due to its potential health benefits.

It is found in small amounts in many fruits and vegetables, including strawberries, apples, persimmons, grapes, and onions.

Fisetin shares some of the anti-aging, disease-fighting properties of other polyphenols. Yet it stands out for its remarkable potency as a **senolytic**.¹⁷

Improved Bioavailability

There's long been a problem with oral fisetin. Soon after ingestion, it is rapidly metabolized in the gut, making it much less effective.

Scientists have now solved this problem by combining **fisetin** with a form of fiber known as **galactomannans**, isolated from the spice **fenugreek**.

This novel formulation has been shown to increase the **bioavailability** (absorption) of fisetin by as much as **25 times**, which may greatly improve its impact on health and longevity.¹⁸



A Powerful Senolytic

Senescent cells are aged cells that stop functioning properly and can cause damage to surrounding tissues. They lose the ability to grow or divide, and they refuse to die off, earning them the name “**zombie cells**.”

These senescent cells spew out compounds that incite harmful systemic **inflammation** inflicting even *more damage*.^{19,20}

Senescent cells are a major driver of age-related disease and dysfunction. They even accelerate the aging process itself.

Senolytics are compounds with the ability to *destroy* senescent cells. They hold great promise in the fight against aging and age-related disease, slowing or even *reversing* the aging process.^{16,17,21,22}

One of the first senolytics discovered was another polyphenol, **quercetin**, which works effectively when coupled with a chemotherapy drug, **dasatinib**.

Fisetin is a more powerful **senolytic** than quercetin. And it works on its own, without the potential side effects of cancer drugs.

A cell study published in the journal *Aging* showed that it eliminated about **70%** of senescent cells—while doing no harm to healthy, normal human cells.²²

Another study tested **10** plant-derived compounds, including quercetin, head-to-head. Fisetin was the **most effective** at eliminating senescent cells, both in cell cultures and in an animal model.¹⁷

These findings suggest **fisetin** may be an effective weapon in the fight against aging.

There are a number of **human** trials of fisetin currently in progress.²³ But an animal study has already shown striking results.

When mice that were the human equivalent of **75** years of age were given **fisetin**, they lived an average of 2.5 months longer. That's close to a **10% increase in lifespan**.¹⁷

Fighting Oxidative Stress and Inflammation

Fisetin promotes longevity in several other ways.

Oxidative stress and **chronic inflammation** accelerate aging processes and increase risk for chronic diseases.

Fisetin is an **antioxidant** and **anti-inflammatory**.

By scavenging harmful free radicals, it *prevents* the damage it does to DNA, proteins, and other cellular components.²⁴



It reduces **inflammation** by shutting off pathways that promote it, and by reducing the production of pro-inflammatory compounds.¹⁰

Mimicking Caloric Restriction

Reducing food intake through a **calorie-restricted diet** has been shown to slow aging, extend lifespan, and improve resistance to disease.²⁵

Research has identified the cellular pathways that are affected by such a diet. Among other benefits, caloric restriction:²⁶

- Reduces the activity of **mTOR**, a protein linked to aging, weight gain, and chronic disease,
- Boosts the function of **sirtuins**, proteins that regulate cellular health,
- Increases the activity of **AMPK**, an enzyme that regulates metabolism, and
- Promotes **autophagy**, cellular “housekeeping.”

Researchers have found that fisetin has a similar effect on **every one** of these pathways, mimicking the effects of **caloric restriction**.^{10,16,27,28}

For example, **sirtuin** proteins shield cells from damage and help keep them in peak form. But sirtuin function diminishes with age, leading to increased susceptibility to disease and rapid aging.^{29,30}

AMPK activity also declines with age, increasing risk for deteriorating metabolic function, obesity, diabetes, and more.³¹

WHAT YOU NEED TO KNOW

The Senolytic Power of Fisetin

- **Fisetin** is a flavonoid found in several fruits and vegetables, including strawberries, apples, grapes, and onions.
- Fisetin is one of the most **potent senolytics** yet discovered among plant-derived polyphenols, destroying dysfunctional **senescent cells** and **extending lifespan** by approximately **10%** in animal studies.
- This compound has been shown in pre-clinical studies to protect against cancer, diabetes, and obesity. In a human trial, it improved outcomes in **stroke** victims.
- Taken orally, fisetin is rapidly metabolized in the digestive tract. Scientists have discovered that combining it with **galactomannans** from fenugreek prevents that from happening.
- A new formulation boosts the bioavailability of oral fisetin by as much as **25 times**, allowing more of it to circulate throughout the body, which may promote longevity and better health.

Several preclinical studies have shown that fisetin *increases* sirtuin function *and* AMPK activity.³²⁻³⁴ This protects cells and keeps them on a youthful and healthy path.

Protecting the Heart

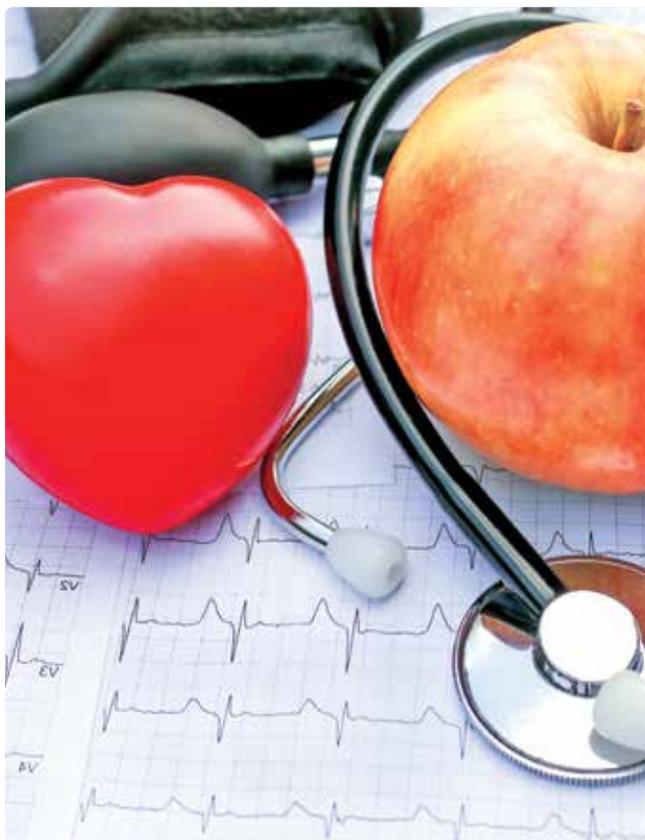
Fisetin not only has the ability to extend lifespan in preclinical models, it may also reduce the risk for many of the most common chronic illnesses.

Heart disease remains the leading cause of death in the U.S. Most common forms of heart disease are due to inadequate flow of blood, oxygen, and nutrients to the heart, which can lead to a **heart attack**.

Over the last two years, studies have demonstrated that fisetin can **protect the heart** from injury. Even after **heart attack** models, heart cells fare better when **fisetin** is present.

In one recent study published in the journal *Nature*, rat heart cells starved for nutrients and oxygen were protected by fisetin, preventing cell death.³⁵

And in animal models of **heart attack**, the extent of heart damage was *reduced* when treated with fisetin, preserving better heart function.^{36,37}



In humans who suffer a heart attack, an **arrhythmia** (abnormal heart rhythm) can often develop.³⁸ In an animal study, fisetin intake after a heart attack significantly reduced the risk of **atrial fibrillation**, a common arrhythmia that increases the likelihood of stroke or heart failure.³⁹

Preventing Obesity and Metabolic Disorders

Fisetin may also help to prevent obesity and common metabolic disorders, like **type II diabetes**.

Obesity predisposes people to higher rates of cardiovascular disease as well as cancer, dementia, and many other conditions.

By *increasing* activity of AMPK and *decreasing* activity of mTOR, fisetin may **reduce weight gain** and protect against related disorders. Even in mice fed a **high-fat** diet, fisetin **prevented weight gain** while protecting the liver, heart, and other organs.^{5,10,40,41}

Rodent models of **diabetes** find that fisetin reduces **body weight** and improves **glucose control** and **insulin sensitivity**.^{4,12,40-42}

Having better **glucose control** can protect against many of the diabetic complications, like kidney disease, eye disease, and neurological disorders.

Life Extension has long suggested the importance of keeping **fasting blood glucose** between **70-85 mg/dL**, which is challenging for most aging people to accomplish. Fisetin may offer a solution to stubbornly high glucose levels.

Fighting Cancer

As an anti-inflammatory, fisetin may lower the risk of developing cancer.⁴³⁻⁴⁶ But fisetin's **anti-cancer** activity goes even further.

Two recent preclinical studies have shown fisetin to be effective in controlling even some of the most aggressive forms of cancer.

In one, scientists investigated the impact of fisetin on human glioblastoma cells.⁴⁷ **Glioblastoma**, a malignant brain tumor, is one of the most invasive and rapidly growing forms of cancer. Even with surgery and chemotherapy, it is usually impossible to control.

Fisetin treatment significantly reduced the growth of glioblastoma cells and even caused them to die off. When directly compared to a chemotherapy drug called **carmustine**, fisetin killed cancer cells at lower doses.

In another recent study, fisetin was effective against several cell lines of **triple negative breast cancer**. This aggressive form of breast cancer is highly resistant to most medical treatments.⁴⁸

In several other studies, fisetin prevented cancer migration and growth while reducing inflammation, enhancing autophagy, and inciting cancer cell death.^{11,49-55}

Fisetin may one day be considered as an adjuvant nutritional approach by progressive oncologists.

Brain Benefits

Fisetin has been demonstrated to be **neuroprotective** in animal models of Alzheimer's disease, Parkinson's disease, ALS (amyotrophic lateral sclerosis), and others.^{1-3,8-10,15}

In a **2019** clinical study, fisetin was found to help in the treatment of a **stroke**.

Strokes typically occur suddenly, without warning, and can lead to permanent loss of brain function. The most effective medical treatments dissolve or remove the blood clot blocking blood flow to the brain.

But the best chance for success comes when treatment is initiated within **three hours** of the onset of symptoms.⁵⁶

Fisetin has been shown to *extend* this treatment window to **five hours**.¹³ While this two-hour extension may not seem huge, it can dramatically increase the number of stroke patients who benefit from clot dissolving and/or clot removing (endovascular thrombectomy) brain-saving therapy.

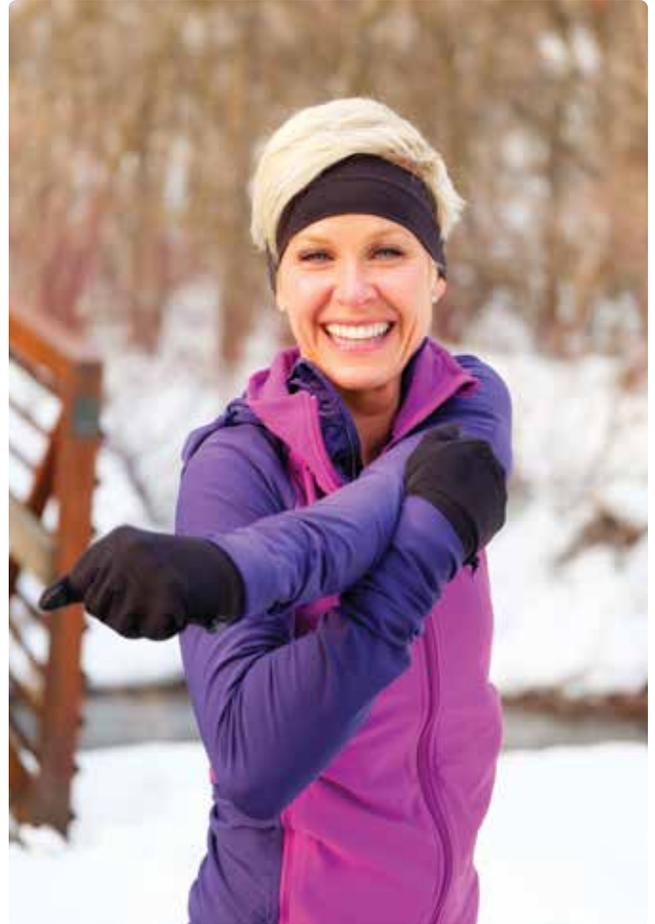
Summary

Fisetin is a flavonoid found in several fruits and vegetables, such as strawberries and apples.

Recent research has found fisetin to be one of the most effective **senolytic** compounds yet discovered among plant polyphenols. By helping to remove dysfunctional **senescent cells**, fisetin may increase longevity and lower risk for disease.

In mice, fisetin intake **increased lifespan by nearly 10%**, even when started late in life.

Combining **fisetin** with compounds isolated from **fenugreek** allows more fisetin to be *absorbed* and distributed in the body to aging tissues that can benefit from its health-promoting actions. •



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b

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c

Probiotics: Know the Facts

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Myth: Probiotics are just for digestive health.

FACT: Probiotics *do* support healthy digestion, but different probiotic strains also support health goals ranging from immune support to heart health. You'll even find a probiotic strain that supports emotional wellbeing!

Myth: More is better when it comes to how much bacteria is in a probiotic.

FACT: It's actually the bacterial strain that determines whether a probiotic is effective. Many supplement brands boast of the billions of colony-forming units in their products—but if they're not offering strains of bacteria

that have been proven to improve your health, you're essentially swallowing billions of nothing.

Myth: The highest quality probiotics need to be refrigerated.

FACT: The most up-to-date technology is shelf-stable.

Myth: One high-quality probiotic every day is all you need.

FACT: Since different probiotic strains provide different benefits, choose the ones you need to maximize *your* personal health goals. Customize your microbiome!

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A probiotic's "strain" helps us tell them apart, and what they do. But how can you tell which one is which? Let's use FLORASSIST® Immune & Nasal Defense's *Lactobacillus rhamnosus* CRL-1505 as an example.

"*L. rhamnosus*" is the scientific name. "CRL-1505" is the strain. There are different strains of *L. rhamnosus*—but CRL-1505 is the one that encourages a healthy immune response.

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d	FLORASSIST® Heart Health <i>Probiotic supplement for heart health</i> 60 vegetarian capsules	01821

	FLORASSIST®	Item #
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- Targets longevity pathways²⁻⁶
- Extends lifespan of mice by about **10%**⁷
- Removes **senescent** cells through **senolytic** action⁷
- Suppresses excess **mTOR** activation⁸

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Just one capsule daily of **Bio-Fisetin** helps manage **senescent cells** and may support overall longevity.

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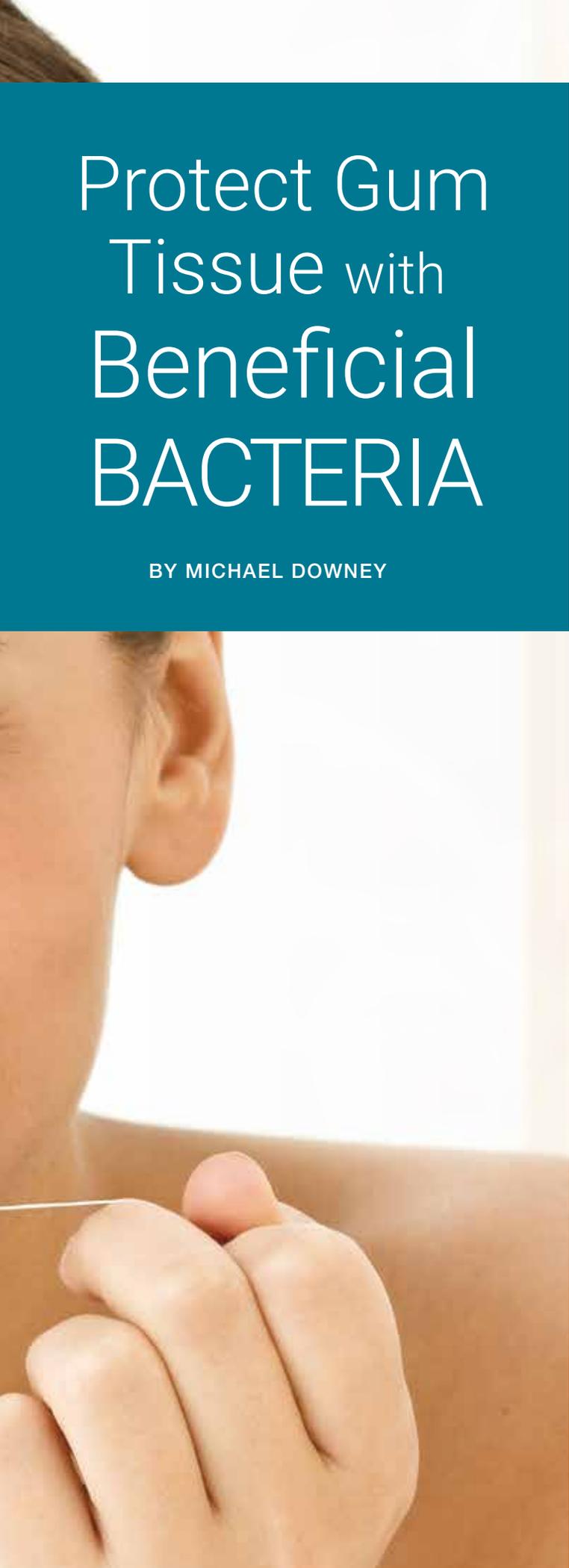


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Protect Gum Tissue with Beneficial BACTERIA

BY MICHAEL DOWNEY

Your oral cavity is teeming with over 700 different species of bacteria.

It is second only to the gut for size and diversity of microbial communities in your body.^{1,2}

An *unbalanced* oral microbiota may contribute to systemic disease conditions.²

Even with daily brushing and flossing, many people still end up with **periodontal disease**, often referred to as **gum disease**.

Researchers have identified a way to reduce gum disease and improve oral health that can provide additional protection beyond daily brushing.^{3,4}

Improving gum health may lower the risk for a host of inflammatory disorders commonly associated with aging.

Gum Disease Threatens the Whole Body

More than **47%** of people over age 30 have **gum disease**. After age 65, the rate rises to a shocking **70%**.⁵

Gum disease, or **periodontal disease**, is associated with disorders throughout the body, including cardiovascular, lung, kidney, bone, and Alzheimer's diseases.

An underlying link is periodontal disease's effect on the **oral microbiota**, the natural community of microbes living in the oral cavity.

When healthy, the oral microbiota supports and protects the delicate mucous membranes as well as the surface of the teeth themselves.

However, inadequate oral hygiene, as well as poor diet and lifestyle factors, drugs, and disease, can disrupt this balance. The resulting microbial imbalance—often called **dysbiosis**—allows excessive growth of pathogenic (disease-causing) organisms in the oral cavity.

This, in turn, disrupts the mouth's immune system and creates a vicious cycle that can have disastrous effects on many body systems,⁶ causing diseases in parts of the body far removed from the mouth itself.⁷

Two Beneficial Bacteria Halt Gum Disease

Probiotics are beneficial live bacteria. They have been used for years to rebalance the **gut microbiota**, supporting the growth of helpful organisms and crowding out harmful ones.

The **oral cavity** holds the *second largest and diverse microbiota* after the gut.¹

Beneficial bacteria reduce the dangerous strains, which allows a wider range and number of beneficial microbes to succeed.

After studying numerous types of bacteria, scientists identified **two specific strains** that can restore oral health and halt the process of periodontal disease.^{3,8,9}

- ***Lactobacillus plantarum* L-137**, which boosts oral immune function and promotes healing, and
- ***Streptococcus salivarius* M18**, which kills harmful oral bacteria and then flourishes.

Beneficial Effects

Scientists conducted research into understanding how these two bacteria promote oral health.

They found that a heat-treated form of ***Lactobacillus plantarum* L-137** could improve the immune system's fighting ability.³

In a rat model of metabolic syndrome, oral treatment with ***L. plantarum* L-137** was shown to have **anti-inflammatory** effects on cardiac and fat tissue. That resulted in *reduced*:¹⁰

- Heart dysfunction,
- Accumulation of fat mass under the skin,
- Insulin resistance (a cause of high blood sugar), and
- Levels of pro-inflammatory **IL-6**.

The probiotic ***Streptococcus salivarius* M18** was shown to:

- Colonize the human mouth to generate healthy bacteria to compete with harmful bacteria,^{8,9}
- Generate bacteria-suppressing weapons called *bacteriocins*, which function like antibiotics at the local level,¹¹⁻¹³ to inhibit tooth and **gum disease**-producing organisms,^{8,12-14}



- Produce the enzymes **dextranase** and **urease**, which break down dental plaque,⁸
- Promote a neutral oral **pH**, which supports the oral microbiota,⁸ and
- Reduce **IL-6**, lowering the inflammation that accelerates gum disease and threatens the body.⁸

Researchers then set out to validate these strains in **clinical** trials.

***L. plantarum* L-137** **Fights Gum Disease**

Scientists conducted a controlled, randomized trial of ***L. plantarum* L-137** on 39 volunteers with chronic **periodontitis**.³

Some participants received a placebo. Others took a capsule containing heat-treated ***L. plantarum* L-137**.³

Researchers used a periodontal probe to measure the **pocket depth**, the distance from the gum line to the bottom of the tiny pocket between the gum and tooth root. Healthy gum pockets are **3 mm** or less, while a depth of **4 mm** or more is clinically defined as **periodontal disease**.¹⁵

After 12 weeks, those treated with ***L. plantarum*** had a **64%** greater improvement in pocket depth than placebo recipients.³

These results demonstrate that periodontal disease can be improved with ***L. plantarum* L-137**.

S. salivarius **Improves Oral Health**

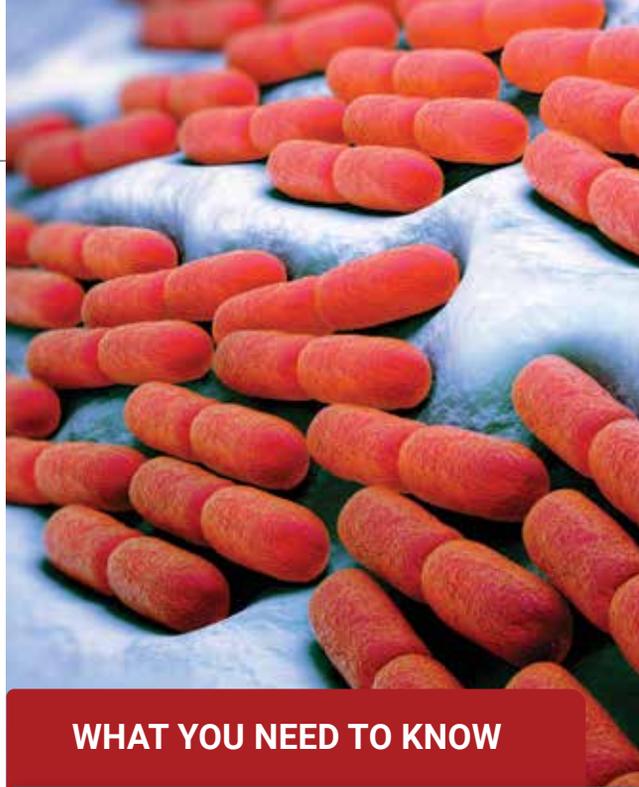
Reducing pocket depth is just one piece of the periodontal disease puzzle, another is dental plaque.

One clinical trial showed that **88%** of ***S. salivarius*** recipients maintained **plaque** scores *lower* than their pretreatment values after a three-month treatment period, compared with **44%** of placebo recipients.⁸

Investigators then conducted a trial to test how ***S. salivarius* M18** affected broader parameters of oral health.⁴

Scientists recruited men and women, aged 20-60, with moderate or severe **gingivitis** (inflammation of the gums) and moderate **periodontitis**.

For 30 days, half received no treatment, and half took lozenges containing **200 million** bacteria of the ***S. salivarius* M18** strain daily after brushing.⁴



WHAT YOU NEED TO KNOW

Beneficial Bacteria Promote Oral Health

- **Gum disease** is extremely common in older adults. It often leads to bleeding gums and tooth loss.
- Gum disease is associated with body-wide health problems, including cardiovascular disease, lung and kidney diseases, cancer, and others.
- Maintaining a healthy and balanced **oral microbiota** protects against gum disease.
- A heat-treated form of the probiotic strain ***L. plantarum* L-137** boosts oral immune function, reducing inflammation and promoting healing.
- The probiotic strain ***S. salivarius* M18** has been documented to rebalance the bacterial populations of the mouth, improving oral health.
- Taken daily, these two beneficial bacteria can help prevent gum disease, enhancing oral *and* total body health.

On the last day of treatment, compared to the untreated group, those in the ***S. salivarius* M18** group had:⁴

- **44%** lower mean **plaque index** scores,
- **42%** lower mean **gingival index** scores (which assess the prevalence and severity of gingivitis),
- **53%** lower modified **sulcus bleeding index** scores (a measurement of gum bleeding), and
- **20%** lower **pocket depth** measurements.

Treatment was then stopped, and measurements were taken 30 days later. Even then, *a month after treatment had ended*, the lozenge group had:⁴

- **37%** lower mean **plaque index** scores,
- **35%** lower mean **gingival index** scores,
- **51%** lower modified **sulcus bleeding index** scores, and
- **22%** lower probing **pocket depth** measurements.

This means that the probiotic lozenge significantly improved periodontal health—and sustained these benefits long after treatment stopped.

Summary

Gum disease affects more than **70%** of older adults. It often leads to tooth loss and is associated with an increased risk of serious disorders throughout the body.

A cofactor in the development of periodontal disease is an imbalance in the normal microbial community of the oral cavity.

Scientists have shown that a heat-treated form of the probiotic strain ***L. plantarum* L-137** boosts oral immune function, reduces inflammation, and promotes healing.

A second probiotic strain, ***S. salivarius* M18**, rebalances the bacterial populations of the mouth, crowding out harmful microbes.

Studies show that these two beneficial bacteria strains help prevent gum disease and protect oral *and* total body health.

The ideal time to initiate **oral probiotics** is after a professional teeth cleaning.



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FLORASSIST® Oral Hygiene provides the *S. salivarius* **BLIS M18™** oral probiotic that colonizes the mouth and inhibits the growth of unwanted bacteria.¹⁻²

This product also contains beneficial Immuno-LP20®.

Just one mint cherry lozenge of **FLORASSIST® Oral Hygiene** a day maximizes oral hygiene by supporting healthy bacterial colonization throughout the mouth.³⁻⁴

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Magnesium's Role in HEART HEALTH

BY MICHAEL DOWNEY





Magnesium is a hard-working mineral.

It helps **300 enzymes** perform vital functions throughout the body.

Magnesium's benefits range from building bone to producing energy and synthesizing proteins.¹

But it doesn't stop there.

It also helps prevent an array of **cardiovascular disorders**.

Dietary surveys have shown **deficient** intake of **magnesium** is epidemic in the United States.

Data from the ***National Health and Nutrition Examination Survey*** show that **48%** of Americans of all ages have intake below the **estimated average requirement**.^{1,2}

Inadequate magnesium levels have been linked with an increased risk for cardiovascular disease, including stroke, coronary heart disease, heart failure, arrhythmias, and death.^{3,4}

Higher blood levels of **magnesium** are associated with a lower cardiovascular disease risk.⁴

Hidden Danger of Low Magnesium

Magnesium is a mineral found in many foods, including leafy vegetables, whole grains, beans, nuts, yogurt, and fish.

But it's difficult to get and **absorb** enough from dietary sources alone.

Approximately **64%** of all men and **67%** of women in the U.S. have inadequate dietary intake of magnesium. Among those above age 71, roughly **81%** of men and **82%** of women have inadequate dietary intake of magnesium.^{5,6}

That's a serious problem.

Magnesium is involved in critical metabolic functions.⁷ This means that myriad bodily systems and functions *depend* on **adequate** magnesium and suffer when **deficiency** occurs.⁵

Adequate magnesium is especially important for healthy and efficient function of **heart muscle** and **blood vessels**.

Recent human studies confirm a strong association between *low* magnesium levels and *higher* heart disease risk.⁵



Correcting Arrhythmias

People with *low* magnesium levels are *more* susceptible to developing **arrhythmias**, potentially fatal disorders of heart rhythm.⁸

Arrhythmias involve abnormal conduction of the electrical impulses that govern heartbeat, causing a beat that is irregular, too fast, or too slow.⁹

Atrial fibrillation, an irregular and often rapid heartbeat, is the leading cardiac cause of **strokes**. This happens when a fluttering **atrial** chamber in the heart causes a clot (thrombus) to form that travels up a carotid artery and blocks blood flow to a portion of the brain. This is called an **ischemic stroke**; the term "ischemia" means "**no blood flow**".

One large study found that people with the lowest blood magnesium levels were approximately **50% more likely** to develop **atrial fibrillation** than those with the *highest* levels. This association occurs even in people *without* cardiovascular disease.¹⁰

Magnesium intake has been shown to correct low-magnesium-related arrhythmias.^{11,12}

For example, intravenous (IV) magnesium is routinely used *before* many heart surgeries that are known to induce postoperative arrhythmias.¹³⁻¹⁷

Oral magnesium is often recommended for those with arrhythmias and low magnesium levels.

Fighting Endothelial Dysfunction

Endothelial dysfunction occurs when the cells lining the inside walls of blood vessels (the **endothelium**) lose normal, healthy function.¹⁸

This promotes the formation of artery-blocking plaque, resulting in **atherosclerosis**, a narrowing of the arteries that restricts blood flow.^{19,20}

In cultured human endothelial cells, magnesium *deficiency* activates the protein complex **NF-κB** (nuclear factor kappa B), a major facilitator of atherosclerosis.²¹

In a randomized, controlled human trial, women aged 40-65, all of whom had high blood pressure and were on diuretic therapy, took either a placebo or **600 mg** of **magnesium** daily.²²

After six months, those taking magnesium had significantly improved **endothelial function**, which led to *reductions* in blood pressure and *increased blood vessel dilation* (widening).

Systolic blood pressure fell, on average, from **144 mmHg** to **134 mmHg**, and diastolic blood pressure decreased from **88 mmHg** to **81 mmHg**.



In addition, the thickness of the carotid artery—a measure of unhealthy arterial thickening—rose in placebo patients but remained unchanged in magnesium-treated patients.²² Thickening of the carotid artery indicates progression of atherosclerosis.

Preventing Heart Failure

Heart failure occurs when the heart doesn't pump enough blood to meet the body's needs.

Currently there are about **6.2 million** adults in the U.S. with **heart failure**.²³

In one study of 22 patients with symptomatic chronic heart failure, an **800 mg/day** dose of magnesium for three months produced a significant *increase* in **arterial compliance** (a measure of how well an artery can relax and contract in response to blood flow).²⁴

This suggests improved **endothelial function** and improved ability of the arteries to deliver oxygen-rich blood to target organs.

Blood levels of magnesium are *also* strongly associated with cardiovascular risk.

An epidemiological study of 3,523 men aged 60-79, with no prior history of cardiovascular disease, demonstrated that **risk for heart failure** declined steadily with rising magnesium levels.²⁵

WHAT YOU NEED TO KNOW

The Cardiovascular Benefits of Magnesium

- **Magnesium** is a mineral needed for at least **300 enzymes** throughout the body to perform their metabolic functions.
- Human studies confirm a strong association between *low* magnesium levels and *higher* risks of **cardiovascular diseases**.
- Almost half of Americans of all ages are below the estimated average requirement for magnesium.
- Human studies demonstrate that taking **oral magnesium** helps ward off cardiovascular problems and supports overall heart health.

Heartburn Drugs Linked to Dangerously Low Magnesium

The U.S. Food and Drug Administration has advised doctors to check patients' magnesium levels *before* prescribing medications known as **proton-pump inhibitors** or **PPIs**.³⁸

Proton-pump inhibitors like Prevacid®, Prilosec®, and Nexium® are taken for the treatment of **heartburn**, also known as **gastroesophageal reflux disease (GERD)**. They are also used to treat peptic ulcer disease.

A scientific review of 35 studies from 2010 to 2018 suggests that, in some people, taking proton-pump inhibitors *causes* low magnesium levels.³⁹

These low levels are associated with increased risk of **cardiac arrhythmias**, and with one often-deadly type in particular, **torsade de pointes** (or **TdP**), which can result in sudden **cardiac arrest**.³⁹

Talk to a doctor about whether to check your magnesium levels before taking proton-pump inhibitors.



Those with the *highest* magnesium blood levels had a **44% lower** risk of heart failure than those with the lowest levels. Higher magnesium levels in this study were associated with reduced markers of **inflammation** and **endothelial dysfunction**.²⁵

Reducing High Blood Pressure

Excess body weight, lack of physical activity, diabetes, and normal aging increase the chances of developing high blood pressure.^{26,27}

A link between magnesium and hypertension has been shown in several human clinical trials.²⁸⁻³⁰

These studies show that the *lower* the magnesium level in patients, the *higher* the systolic blood pressure.

One meta-analysis of trials that enrolled more than 2,000 subjects, found that supplementation with magnesium reduced **systolic** and **diastolic blood pressure** in hypertensive patients.³¹

Those who fail to achieve optimal systolic blood pressure under 120 to 130 mm Hg should consider an anti-hypertension drug like telmisartan.

Lowering Heart Attack and Stroke Risk

Human studies also demonstrate an association between *low* magnesium and *increased* risk of heart attack and stroke.^{6,32-35}

In one analysis of human trials that included a whopping **241,378 participants**, researchers found that every **100 mg of magnesium** in the daily diet was associated with an **8% lower** risk of **stroke**.³⁴

A similar association was found in a later published meta-analysis.³⁵

Combating Coronary Artery Disease

Coronary artery disease occurs when the arteries to the heart become narrowed due to atherosclerotic plaque. This reduces blood flow and significantly boosts the risk of a heart attack.

It is the leading cause of death in men and women in the U.S.³⁶

Magnesium intake has been shown to improve heart function *and* exercise tolerance in patients with coronary artery disease.

In one study, scientists gave 53 men with coronary artery disease **365 mg of oral magnesium citrate twice daily**. After six months, they had improved oxygen utilization during exercise and greater pumping action in their left ventricle, the heart's main pumping chamber.³⁷

These effects indicate that magnesium improved blood flow and oxygen delivery in these patients.

Summary

The mineral **magnesium** is vital for **heart health**.

More than **80%** of people over **age 71** have inadequate dietary intake of magnesium, placing them at risk for serious cardiovascular events.

Cardiovascular disease, including stroke, coronary heart disease, heart failure, arrhythmias, and even death, has been associated with inadequate magnesium levels.

Low-cost **magnesium supplements** offer an easy solution to replenish this essential mineral. •

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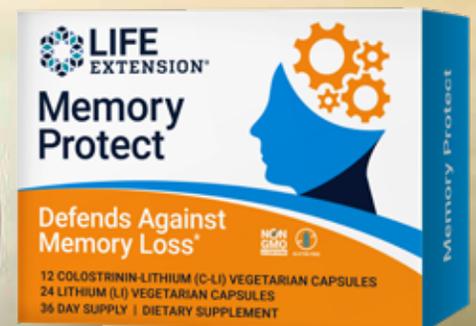
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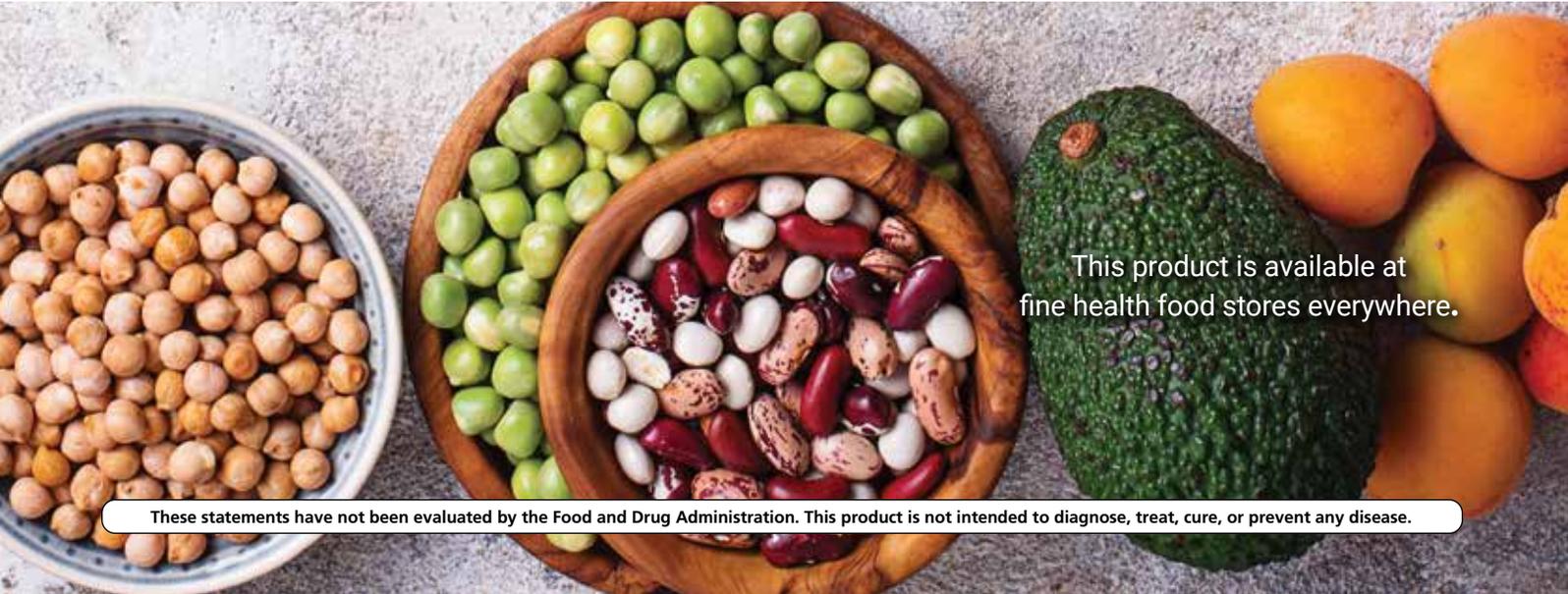
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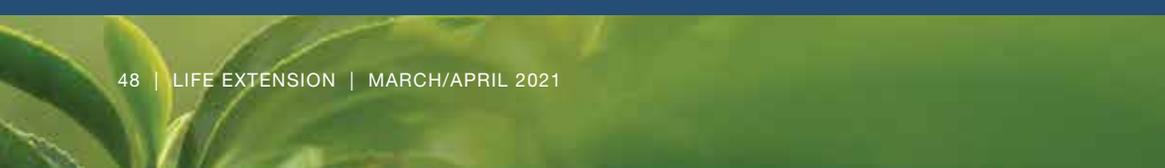
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Plant-Derived Compounds that Reduce Chronic Stress

BY STACY KELLER





Doctors are increasingly recognizing the role that **chronic stress** plays in our health and immune systems.

Heart disease, digestive disorders, diabetes, cancer, and most importantly, our immunity can all be impacted by chronic stress.¹⁻⁴

Over the past year Americans have reported feeling an extraordinary amount of stress affecting their well-being.⁵

Reducing the impact of stress has long been recognized as a significant aspect of any wellness program.

Scientists have identified two **plant extracts** that work to reduce stress and anxiety levels.

An amino acid called **theanine**, found in tea leaves, has been shown in clinical trials to relieve chronic stress.⁶⁻⁸

Lemon balm, an herb in the mint family, induces calm and **lowers anxiety** levels.^{9,10}

Stress Impairs Immunity

In addition to its adverse effect on emotional wellbeing, **chronic stress** may shorten healthy lifespans via several detrimental pathways.^{11,12}

Chronic stress **suppresses the immune system**, impairing the function of infection-fighting immune cells.^{2,13}

It also spurs a long-lasting release of the steroid hormone **cortisol** and other signaling molecules that further weaken immune responses.²

Chronic stress is associated with increased levels of damaging **inflammation**.^{13,14}

Chronic stress is also a factor in many cases of anxiety and depressive disorders.

The World Health Organization has ranked depressive and anxiety disorders as the **first** and **sixth** most important contributors, respectively, to non-fatal negative health outcomes.¹⁵

There are proven ways to reduce stress, including exercising, eating a healthy diet, and getting adequate sleep.

Scientific research has also identified **nutrients** capable of reducing the stress we feel and the harm that stress does to our body.

Theanine Decreases Stress

Theanine (also known as “L-theanine”) is an amino acid primarily found in **green tea**.^{6,7,16-18}

Research suggests that its stress-fighting benefits come from its ability to modulate **neurotransmitters** and **hormones** that change how the body responds to **chronic stress**.^{19,20}

Theanine *inhibits* the activity of the excitatory neurotransmitter **glutamate**, which rises during stress. It does this by blocking glutamate from binding to receptors in the brain.^{17,18}

In a 2019 literature review, researchers present studies showing that a daily dose of theanine, ranging from **200 mg to 400 mg**, has **anti-stress** and **anti-anxiety** effects that work for both short-term and chronic stress.¹⁶

Effects on Chronic Stress

In a study of the impact of **theanine** on **chronic stress**, students in an intense pharmacy-practice program took either **200 mg** of theanine twice daily or a placebo, starting one week before the program and lasting 10 days into it.⁷

The subjects were asked how much stress they felt.





Measurements were also taken of levels of the enzyme **alpha-amylase** in their saliva. *Higher* levels indicate *increased* levels of stress.⁷

The theanine-treated students had reduced salivary *alpha-amylase* and reported feeling significantly less stress than placebo recipients.

In another chronic-stress study, **200 mg** of theanine daily for four weeks significantly reduced measures of stress and anxiety, while improving sleep quality.⁸

Lemon Balm Promotes Calm

Lemon balm is an herb with a long tradition of medicinal use for alleviating stress, anxiety, and insomnia.^{9,21,22}

Lemon balm has been shown to *promote* activity of the neurotransmitter **GABA** (gamma-aminobutyric acid).¹⁰ GABA counteracts the stress-reinforcing effects of **glutamate** in the brain and is associated with a more calm, relaxed state.^{23,24}

Studies using **600 mg** of standardized lemon balm extract have shown that it improves mood and lowers perceived stress.^{9,10}

WHAT YOU NEED TO KNOW

Lower Stress for Improved Immunity

- Over the past year Americans have reported feeling an extraordinary amount of stress that is affecting their well-being.
- The amino acid **theanine**, found in tea leaves, has been shown in clinical trials to relieve **chronic stress**.
- The herb **lemon balm** also induces calm and lowers **anxiety** levels.
- Controlling the impact that chronic stress has on the body is an essential part of any wellness program.

Summary

A combination of **theanine** and **lemon balm** can ease stress and its damaging effects, without causing drowsiness or loss of alertness.

The amino acid theanine inhibits the action of **glutamate**, an excitatory neurotransmitter that is involved in stress. Excess excitatory stimulation injures neurons.

Lemon balm, an herb in the mint family, complements that activity by increasing the action of **GABA**, a neurotransmitter that *opposes* the stressful effects of glutamate and promotes a feeling of calmness.

These two nutrients can help relieve stress and anxiety and reduce their harmful impact on our body. •

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GREEN TEA'S Neuroprotection Benefits

BY SHELDON CANNON



Scientists are finding that compounds found in **green tea** can bolster and protect brain health.¹⁻⁴

One meta-analysis found that the rate of cognitive disorders was **35%** lower in people who regularly drank tea.⁵

Parkinson's disease risk was reduced by **26%** for every **two cups per day** of tea consumed in another study.⁶

The healthful compounds found in green tea work in several different ways to boost brain function and guard against cognitive decline.

For those who do not consume enough green tea, standardized **extracts** provide the beneficial polyphenols called **catechins**.

Green Tea Medicine: Catechins

The tea plant, *Camellia sinensis*, is packed with the health-promoting compounds known as **catechins**.

One of the most abundant and widely studied catechins in green tea is **epigallocatechin gallate (EGCG)**.

Studies of whole tea consumption, extracts of green tea, and individual isolated catechins, have all demonstrated health benefits.⁷⁻¹³

Scientists have identified scores of mechanisms by which green tea wards off disease and the ravages of aging.

The widespread consumption of green tea has led to large observational studies that evaluate its association with risk for various disorders, including age-related cognitive decline.

Improving Brain Performance and Mood

Many of these effects of green tea help maintain strong mental function well into the future. But it also has *immediate* effects that improve brain function *now*.

Researchers used memory tasks and an advanced imaging technology called **functional MRI** to evaluate

cognitive functions in healthy volunteers.¹⁴ They found that people who were given a **green tea** extract performed better on memory tasks. They also observed enhanced connectivity between areas in the brain involved in the tasks.

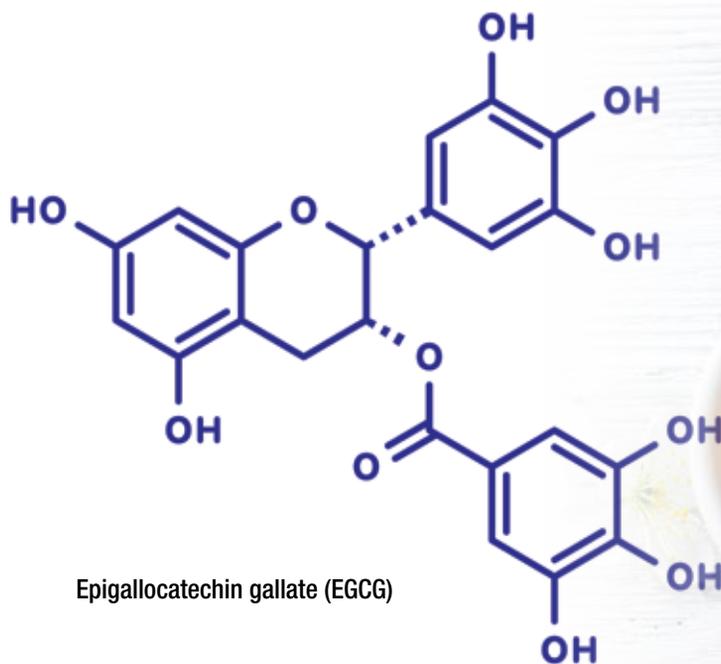
This means they were able to demonstrate *physiological changes in the brain* that correlated with improved mental function.

Another study, using an electroencephalogram to monitor brain activity, saw an overall *increase* in brain wave activity after consuming an EGCG (green tea extract) supplement.¹⁵

Cognitive enhancement isn't the only mental function impacted by green tea. In studies in healthy adults, green tea also **reduced psychological stress**, including feelings of anxiety and depression, and led to a feeling of calmness.^{15,16}

Cognitive Impairment, Alzheimer's, & Dementia

Studies in humans have demonstrated a clear association between tea consumption and a lower occurrence of cognitive disorders, including everything from mild cognitive impairment to Alzheimer's.^{5, 17-20}



One of the largest studies, a pooled analysis of 52,503 participants in countries around the world, found that tea significantly *reduced* the rate of multiple kinds of **cognitive disorders** by **35%**.⁵

Another large meta-analysis evaluated the risk of cognitive disorders in 48,435 individuals.¹⁹ Overall, *higher* tea intake correlated with a significant *reduction* in **cognitive disorders**.

However, when researchers further analyzed these results, they found that **green tea** consumption was more reliably associated with the cognitive benefit than oolong or black tea.

The rate of cognitive disorders in habitual drinkers of **green tea** was **36%** lower than in non-habitual drinkers. Scientists also found a dose-response relationship: The *more* green tea consumed, the *greater the protection* from cognitive dysfunction. In practical terms, those who drank **16 ounces** of green tea per day derived nearly six times more protection from development of cognitive disorders than those who drank **3.5 ounces**.

Other studies have examined tests of cognitive *function*, rather than diagnoses of cognitive disease.^{17,18}

In older adults, green tea was associated with superior performance on these tests. Green tea drinkers scored better for overall cognition, memory function, executive function, and the speed of information processing. And once again, *more* tea intake was linked to *higher* scores.

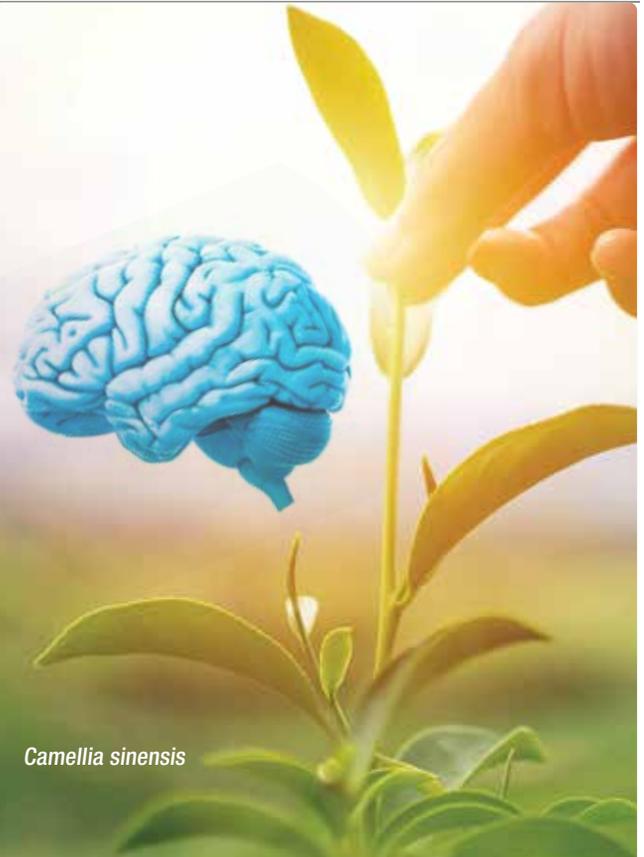
Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder that mostly affects nerve cells in the brain that produce the neurotransmitter dopamine.

It's marked by a progressive loss of motor function, creating difficulties including tremors, slowed movement, and difficulty initiating movements. In more advanced cases, cognitive loss occurs as well, leading to slowed thinking and dementia.

Case-control studies in non-western populations demonstrate a strong protective effect of tea against the development of Parkinson's disease.²¹⁻²³ Up to a **41%** lower rate of Parkinson's was found when comparing those who routinely consume the largest amounts of tea with those who rarely drink tea.

A large meta-analysis included data from a whopping 344,895 individuals all over the world.⁶ As was observed in the studies of cognitive disorders, researchers noted that the *amount* of green tea



Camellia sinensis

WHAT YOU NEED TO KNOW

Green Tea

- Green tea polyphenols have been associated with many diverse health benefits.
- In the brain, green tea offers neuroprotective effects and shields the brain from age-related decline by boosting the creation of *new* brain cells and neural connections.
- Green tea also reduces the risk for neurodegenerative disorders such as Alzheimer's and Parkinson's disease.
- Many large, human studies have demonstrated that green tea intake is significantly associated with reduced risk for age-related cognitive decline and dementia.

intake correlated with the *degree of protection* from Parkinson's disease. In fact, they found that risk of Parkinson's was reduced by **26%** for every **two cups** per day consumed. This effect was more pronounced in European and Asian populations.

Functional Disability

One large, prospective study evaluated the impact that green tea can have on functional disability, regardless of the underlying cause.²⁴ Almost 14,000 Japanese individuals over the age of 64 were followed over time. Researchers found a significant protective effect of greater green tea intake, *reducing* the risk for disability and the need for support for daily activities.

Yet again, the *more* tea a person consumed, the *greater* the protection observed. Those who drank **five or more cups** per day were **33%** less likely to have a significant functional impairment than those who consumed **less than a cup** per day. It's difficult to consume this much green tea but extracts typically contain the amount of polyphenols equivalent to many cups.

Summary

Green tea and its extracts are widely recognized for their numerous health benefits.

In the nervous system, **green tea** provides many protective effects, including:

- Boosting **neurogenesis** (the creation of new brain cells) and **neuroplasticity** (the ability of the brain to adapt) into old age,^{13, 25-33}
- Shielding from the progressive damage that leads to **neurodegenerative** disorders,^{2, 34-38} and
- Offering **neuroprotection** against injuries such as stroke and head trauma.^{29, 39-42}

In the short term, green tea also boosts cognitive function, supporting attention, focus, improvement in mood, and enhanced memory.

Large studies in humans have demonstrated that green tea and its extracts are capable of guarding against age-related brain dysfunction and risk for dementia.





While drinking **five or more cups** of tea per day is difficult, green tea extracts that provide high quantities of polyphenols (catechins) are available in capsule form. Green tea extracts are available in decaffeinated forms, for those sensitive to caffeine.

For those interested in the biological mechanisms that enable green tea to confer brain protection, turn to the next two pages.

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(References continue on page 64.)

HOW GREEN TEA HELPS THE BRAIN

Green tea has been found to offer multiple beneficial effects for health and metabolism that support whole-brain health.

Boosting Neurogenesis and Neuroplasticity

When we're young, our brains operate at peak performance.

Neurogenesis, the growth of *new* brain cells, occurs in the greatest amount during the embryonic stage and continues throughout adulthood. But it wanes with advancing age.

Neuroplasticity, the brain's ability to adapt and form new neural connections, is critical to learning and maintaining memory and other cognitive functions. It also decreases as we grow older.

Green tea can support both neurogenesis *and* neuroplasticity.

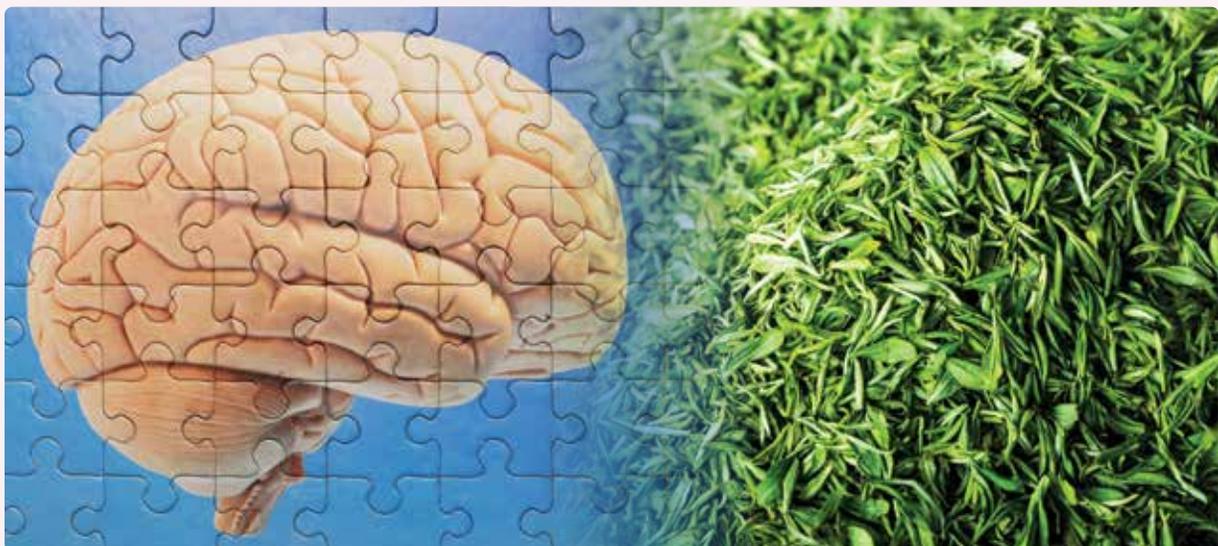
In animal models and in cell cultures, it's been shown to *stimulate* neurogenesis.²⁵⁻²⁷ In studies like these, EGCG supported new brain cell growth and survival in the hippocampus, a

part of the brain critical for the formation of new memories.^{25,28} In an animal study, it also aided stem cell growth in the brain after a traumatic injury.²⁹

One of the most important mediators of neuroplasticity is a growth factor called brain-derived neurotrophic factor (BDNF). Its levels tend to diminish in old age,³⁰ impairing the ability of the brain to adapt and resist injury.

Green tea has the ability to *stimulate* production of BDNF to help maintain optimal brain function.

In one study, the drop in BDNF levels in aging rat brains was *prevented* by supplementing their diet with green tea.³¹ And in older mice, green tea supplementation prevented the decline in BDNF levels and alleviated learning and memory deficits associated with aging.^{13,32,33}





Protection from Age-Related Damage

Cognitive disorders are a terrifying scourge of old age. The two most common are **mild cognitive decline** and **Alzheimer's disease**, the most prevalent type of **dementia**.

The pathology in the brain associated with these disorders includes the deposition of abnormal proteins that accumulate to toxic levels. These proteins, including **beta-amyloid** and **hyperphosphorylated tau**, create the plaques and tangles that cause cognitive function to slow dramatically in Alzheimer's patients.

They also incite neuroinflammation, leading to further injury and cognitive decline.

Green tea protects against these age-related threats in a number of ways.

In several animal studies, green tea was found to significantly *reduce* the build-up of both these toxic proteins, and even to aid in clearing them from brain tissue.³⁴⁻³⁶ Reduction of amyloid and tau deposits in these studies protected cognition, preventing age-related memory and learning deficits.

Green tea also has powerful anti-inflammatory effects in the nervous system, acting to reduce the harmful neuroinflammation associated with these diseases.³⁷

Parkinson's disease has been found to respond to supplementation with green tea as well.² The buildup of **alpha-synuclein** and resulting neuroinflammation and neurotoxicity associated with this disease is *also* reduced by green tea.³⁸

Guarding Against Strokes and Injury

Cognitive disorders aren't the only risks to brain function in later life. Damage to the brain is also common from strokes and head trauma.

Strokes occur most often as a result of blood vessel disease, which can cause either a blockage of blood flow to the brain or bleeding into the brain. These typically occur suddenly and without warning.

Green tea intake can **reduce the risk of brain damage** from strokes in multiple ways. For one, green tea's cardiovascular health benefits help prevent blood vessel disease in the first place. This lowers the risk, not only for stroke, but also for coronary artery heart disease and other conditions.^{39,40}

Green tea can also provide a **neuroprotective** effect, reducing the impact if an injury *does* occur. This was demonstrated in a recent study in rats that had suffered a stroke, which found that green tea reduced the severity of injury.⁴¹ The degree of tissue necrosis (death), oxidative stress, and cognitive deficits were all lowered by tea, and the neuroprotection was greater with green tea than other types of tea.

Neuroprotection of this type is also observed in animal models of **head trauma**. Green tea reduces both the severity of injury *and* the functional deficits that result.^{29,42,43}

(Scientific references are on the previous and following pages.)

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The numbers of **synapses** that connect brain cells decline with aging.

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These products are available at fine health food stores everywhere.

Reference: **Gerontology*. 1996;42(3):170-80.

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

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Also available are **10 mg PQQ** (Item #01500) and **100 mg Super Ubiquinol CoQ10 with PQQ** (Item #01733).



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- Improves cognitive performance³
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Mega Green Tea Extract Lightly Caffeinated

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100 vegetarian capsules



* **EGCG** is the acronym for **epigallocatechin gallate**, which is the polyphenol in green tea that has demonstrated the most robust health benefits.

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These products are available at fine health food stores everywhere.

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New England Journal of Medicine Cites Benefits of Intermittent Fasting

BY SUSAN PALMER



Scientists continue to unravel the benefits of **caloric restriction** and **intermittent fasting**.

The simple act of limiting food intake increases lifespan in animal models and reduces age-associated disorders such as diabetes and heart disease.¹⁻⁴

A report published in the ***New England Journal of Medicine*** reviewed extensive research on **intermittent fasting** and caloric restriction. Multiple mechanisms were identified by which these dietary changes are expected to have a beneficial impact on health.³

The report found three different **intermittent fasting regimens** to be *just as effective* as true fasting at inducing benefits of **caloric restriction**.

Intermittent fasting, also known as **time-restricted eating**, helps regulate the expression and activity of proteins and other cell factors known to influence health and aging.

Those able to adjust their time of food intake may experience biological changes that boost resistance to disease and help extend lifespan.

Types of Intermittent Fasting

Modern humans have gotten used to eating three meals a day along with frequent snacks.

This constant intake of food has profound adverse effects on our metabolism and health.

Digesting and processing food is a complex, energy intensive process that can accelerate pathological aging processes.

Studies have consistently shown that **intermittent fasting** is superior to constant eating in many ways.

All **intermittent fasting** regimens have regular periods of eating when food and calories are *not* restricted. But their benefit comes from restricting the amount of time that one is eating, and alternating it with relatively long periods of not eating or eating very little.

Three types of intermittent fasting that have been most studied in animal models and human trials and discussed in the *New England Journal of Medicine* are:^{3,5}

- 1. Alternate-day fasting.** In this regimen, food intake is normal for one day followed by a day of fasting or severe caloric restriction. The pattern is continued indefinitely.
- 2. Time-restricted feeding.** In this model, intake of food is restricted to only a small number of hours per day. The rest of the day is spent fasting. One common pattern is to restrict food intake to **six hours** during the day, while fasting the remaining **18 hours**. (Other programs advocate for about 16 hours a day of fasting and an eight-hour eating period.)
- 3. 5:2 intermittent fasting.** One of

the most popular forms of intermittent fasting restricts calories (with a limit of **500-700 calories** per day) on just **two days** of each week. Normal food intake is fine on the other five days.

These **intermittent fasting** plans are often easier to adhere to than daily **caloric restriction**.

These three patterns of eating are believed to be equally effective for improving health.

Understanding Fasting

The **fed state** is the period of time when food has recently been consumed.

The **fasting state** occurs after several hours without eating, when nutrients are less available and the body must conserve energy and resources.

Cell metabolism changes dramatically between these two different states.

In the **fed state**, when nutrients

are plentiful, energy is *stored*, often as **fat**.

In the **fasting state**, as carbohydrates from previous meals are used for energy, fat and other energy-storage compounds are *broken down*.

Some of these fats are converted by the liver into **ketones**, substances that provide an alternative fuel source for the brain and other tissues.

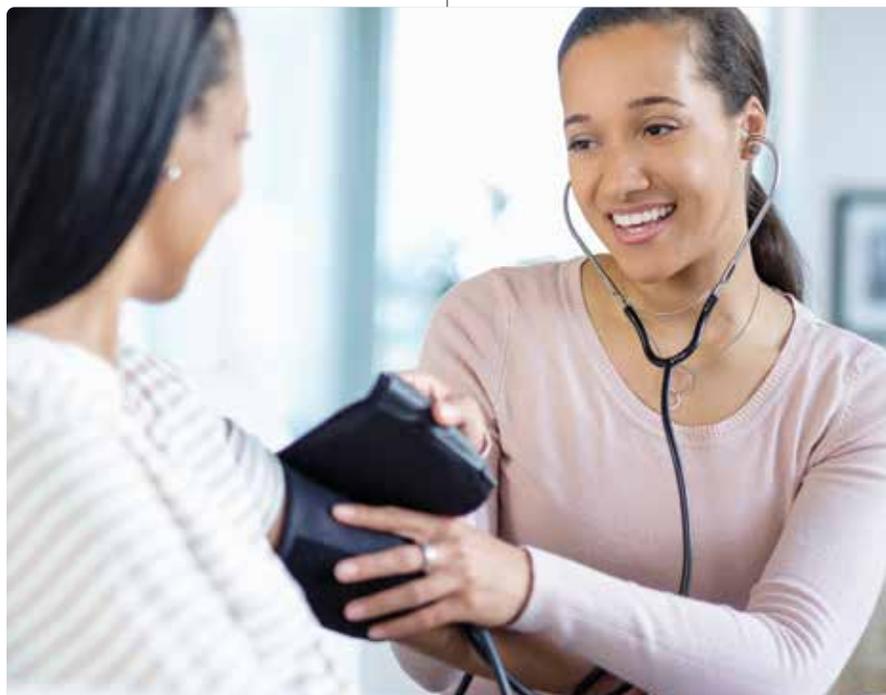
This metabolic shift to ketone metabolism takes time. Ketones in the blood begin to rise **8 to 12 hours** after fasting begins.³ Most people who eat throughout the day, every day, *never* enter a **fasting state**.

Changes in the Fasting State

When energy availability is low during a **fasting state**, critical changes occur in cellular function.

One of the chief proteins governing cellular processes is known as **mTOR**. During fasting, the activity of mTOR decreases.

This leads to an *increase* in





Intermittent Fasting from Dawn to Sunset for Four Consecutive Weeks Induces Anticancer Serum Proteome Response and Improves Metabolic Syndrome

- No eating /drinking between dawn and dusk—**14-15 hours** each day
- Average **7.25 pounds** of **weight loss**
- Average **8 mmHg** reduction in **blood pressure**
- Significant increase in **tumor suppressor/anticancer proteins**
- Significant decrease in several **tumor promoter/pro-cancer proteins**
- Increase in a protein called **calreticulin** (by around **16 times**)
- Calreticulin enhances **IgG** response to a **SARS-CoV** spike protein

Sci Rep. 2020 Oct 27;10(1):18341.

autophagy, a cellular “housekeeping” process that removes damaged proteins and other cellular debris. Autophagy helps to keep cells functioning optimally.³

At the same time, the activities of several other cellular functions are *increased* in a **fasting state** including:³

- **AMPK**, which regulates metabolism and energy use,
- **Sirtuins**, which protect against age-related decline and promote longevity, and
- **FOXOs**, which help regulate the expression of genes involved in cell growth, insulin regulation, and longevity.

Increased activity of *each* of the above-mentioned has been tied to longevity and resistance to disease.

Together, they protect cells by repairing DNA, replacing damaged cell parts, producing more mitochondria, and reducing inflammation.³

These changes in response to fasting make cells more resilient, healthier, and less prone to disease.

In fact, every one of these functions is being individually investigated by scientists with the goal of extending human life. **Calorie restriction** and **intermittent fasting** positively impact them all.

How Fasting Affects Obesity and Diabetes

Intermittent fasting has been shown to improve metabolism, improving several risk factors for diabetes and heart disease.

Most studies in animals and humans have found that intermittent fasting diets can lead to **weight loss**.⁶

A review of nine studies found that intermittent fasting regimens led to an average **3% to 8%** reduction in body weight over 3 to 24 weeks.⁷

In one study, subjects lost **2.5%** of their initial weight and **4%** of their fat mass in **only 22 days**.⁸ This is especially remarkable considering that these subjects were *not* obese to begin with.

Intermittent fasting has been demonstrated to *reverse* **insulin resistance** in adults who suffer from prediabetes or full-fledged diabetes.^{9,10} In one study, **fasting insulin levels** decreased by **57%**.⁸

Multiple Benefits of Caloric Restriction and Intermittent Fasting

Besides improving insulin sensitivity, caloric restriction and intermittent fasting have been shown to lower blood pressure, heart rate, cholesterol levels, and triglyceride levels.^{1,2}

Intermittent fasting also reduces **inflammation**,¹¹ which is a major contributor to **atherosclerosis**, the buildup of plaque in the arteries.^{12,13}

In animal studies, caloric restriction both prevents the formation of tumors and slows the growth of existing **cancers** of various types.¹⁴⁻¹⁶

Caloric restriction has been found to have cognitive benefits as well, improving verbal memory, working (short-term) memory, higher-level executive function, and overall cognitive function in human trials.¹⁷⁻¹⁹

In animal models of **Alzheimer's** and **Parkinson's** disease, intermittent fasting has been shown to protect brain cells.^{20,21}



A Conflicting Intermittent Fasting Study

The data we are reporting are based on an extensive review article published on **December 26, 2019**, by the *New England Journal of Medicine*.³

This *New England Journal of Medicine* article described previous studies showing systemic health improvements in **humans** who restrict food intake to around **six hours** each day. This means they fasted for about **18 hours** on most days.

The authors of this *New England Journal of Medicine* article outlined prior studies demonstrating how **intermittent fasting** reduces **abdominal fat** while simultaneously improving most measures of disease risk.³

A randomized controlled trial published September 28, 2020, in the *Journal of the American Medical Association* (JAMA) was specifically designed to examine the effects of intermittent fasting on weight loss and metabolic risk markers.

The intermittent fasting group in this trial lost a little weight over 12 weeks, while the three-meal/day control group did not lose a statistically significant amount of weight. This study did not find a significant effect on metabolic risk markers.²²

We've identified reasons why the *JAMA*-published trial did not find the metabolic benefits reported in a review article just 10 months earlier in the *New England Journal of Medicine*.

We at **Life Extension**[®] have long known that **time-restricted eating** (intermittent fasting) does not induce much **weight loss** in those who do not also reduce their overall **calorie intake**.

The preponderance of published evidence, however, continues to support the benefits of **intermittent fasting**. This includes improved **glycemic markers** such as **fasting insulin**. Elevated fasting insulin can impede **weight loss**.^{10,23,24}

On **October 27, 2020**, a subsidiary of the scientific journal *Nature* reported on a **human** study that only required fasting **14-15 hours** each day.²⁵ The study group was in poor overall health, with most suffering from nonalcoholic fatty liver disease.

In just four weeks average weight loss was **7.25 pounds**. Even more impressive were significant improvements in cellular proteins that **protect against cancer**.

The box on the previous page summarizes this study showing potential cancer-prevention effects in response to an easier to adhere to fast of **14-15 hours** a day.

In other conditions, notably asthma and multiple sclerosis, clinical evidence suggests that intermittent fasting can help reduce symptoms.³

Summary

Caloric restriction and **intermittent fasting** activate proteins and induce metabolic changes that rejuvenate our cells and tissues.

Many studies have shown that these changes prolong life in animals, and reduce risk for many age-related chronic diseases, including cardiovascular disease, cancer, and dementia.

Intermittent fasting is easier for most people to adhere to than traditional fasting and can deliver many of the same benefits. •

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*The same nutrients sold
separately would cost
2-3 times more money!*

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Promote Smoother, Youthful-Looking Skin from the Inside Out

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One reason is loss of **ceramides** that are required for skin to retain its **moisture** and youthful suppleness.

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Contains wheat. Gluten free.

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Love the **YOU** in the Mirror

AMPK is an enzyme in the body that signals cells to burn fat for energy.

Over time, AMPK levels decline and can cause accumulation of **abdominal fat**.

AMPK Metabolic Activator:

- Revitalizes youthful AMPK activity
- Encourages use of abdominal fat for energy
- Promotes healthy cellular metabolism



Item #02207

30 vegetarian tablets



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This supplement should be taken in conjunction with a healthy diet and regular exercise program. Individual results are not guaranteed, and results may vary.

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Food Fix

*How to Save Our Health, Our Economies,
Our Communities, and Our Planet—One Bite at a Time*

BY MARK HYMAN, MD



Reversing the global epidemic of chronic disease, healing the environment, and reviving economies, can all be accomplished through, in one word: Food.

In his latest book, *Food Fix*, Mark Hyman, MD, Cleveland Clinic doctor and best-selling author, explains how our current agriculture policies are driving chronic disease, climate change, poverty, violence, and more.

According to Hyman, ultraprocessed foods kill **11 million** people every year and make **60%** of Americans sick with a chronic disease.

How we grow food is the number one cause of climate change—and the culprit behind the alarming loss of soil, water, biodiversity, and pollinators.

Due to current farming practices, it is estimated that the world will run out of topsoil in just 60 more harvests. No topsoil means no food.

We are depleting fresh water sources at **one trillion gallons** more per year than can be replenished by rain.

According to Dr. Hyman, we don't need to fix the food system for a better future; we need a food fix for a *future*.

Fortunately, there are solutions.

In addition to highlighting the enormity of the problem, *Food Fix* provides practical solutions for creating healthier individuals, healthier farming practices, and ultimately a healthier planet.

In this interview with *Life Extension*[®], Dr. Hyman talks about why we desperately need a “food fix”—and provides specific suggestions for ways to restore the broken system.

—LAURIE MATHENA

LE: Why are we in such desperate need of a “food fix?”

Dr. Hyman: Our most powerful tool to reverse the global epidemic of chronic disease, heal the environment, reverse climate change, end poverty and social injustice, reform politics, and revive economies is food.

The food we grow, how we grow it, and the food we eat have tremendous implications not just for our waistlines but also for our communities, the planet, and the global economy.

Chronic disease is now the single biggest threat to global economic development. Lifestyle-caused diseases such as heart disease, diabetes, and cancer now kill nearly 50 million people a year, more than twice as many as die from infectious disease.

Lobbyists’ influence over policy makers has put corporations, not citizens, at the center of every aspect of our food system, from what and how food is grown to what is manufactured, marketed, and sold.

When money rules politics, it results in our current uncoordinated and conflicting food policies, which subsidize and protect and facilitate Big Food’s and Big Ag’s domination of our food system to the detriment of our population and our environment.

LE: How do these companies have such a big influence on the system?

Dr. Hyman: Big Ag and Big Food co-opt politicians, public health groups, grassroots advocacy groups, scientists, and schools, and pollute science and public opinion with vast amounts of dollars and misinformation campaigns.

The consolidation and monopolization of the food industry over the last 40 years from hundreds of different processed-food companies, seed companies, and chemical and fertilizer companies into just a few dozen companies make it the largest collective industry in the world, valued at approximately \$15 trillion, or about **17%** of the entire world’s economy.

And it is controlled by a few dozen CEOs who determine what food is grown and how it is grown, processed, distributed, and sold. This affects every single human on the planet.

We are also depleting nature’s capital—capital that, once destroyed, may only be able to be partially reclaimed. The threat is not only to our health and our children’s future, but also to the health of the planet that sustains us.

Our industrial agricultural and food system is the single biggest cause of climate change, exceeding all use of fossil fuels.

Current farming practices may cause us to run out of soil and fresh water in this century. We are destroying our rivers, lakes, and oceans by the runoff of nitrogen-based fertilizers, which is creating vast swaths of marine dead zones.

LE: How do current farming practices impact our health?

Dr. Hyman: Eleven million people die every year from a bad diet. And more than a billion people in the world are overweight and sick from eating our processed, industrialized diet and not eating a healthy, whole foods diet. In fact, the number one factor causing these deaths is the lack of fruits and vegetables in our diet.

The sad thing is that in America only **2%** of our farmland is used to grow fruits and vegetables, despite our government’s recommendations that **50%** of our diet should be fruits and vegetables.

Fifty-nine percent of our farmland is used to grow commodity crops (corn, wheat, soy) that get turned into ultraprocessed foods that we know are deadly. These processed foods make up about **60%** of our diet!





Why does this matter? For every **10%** of your diet that comes from processed food, your risk of death goes up **14%**. That means a lot of extra deaths because we support agriculture that creates food that makes us sick and fat and harms the environment, and not the production of fruits and vegetables and whole foods that make us healthy.

The complexity of the problem prevents people from connecting the dots and taking action. And most of the true costs are not even recognized, limiting the motivation to change the system.

LE: What is the economic impact?

Dr. Hyman: The World Economic Forum estimated that between 2010 and 2030 the global health care costs for chronic disease will exceed \$47 trillion.

They declared this the single biggest threat to global economic development. General Motors spends more on health care than on steel, and Starbucks spends more on health care than on coffee beans!

Any way you slice it, the costs of obesity and chronic disease are weighing the world down. There is little health care infrastructure, few doctors and nurses to treat these problems, and even less money. The “cheap” food that causes disease is not so cheap after all.

LE: How do America’s food policies impact this situation?

Dr. Hyman: If I had to describe the state of America’s food policies in one word, it would be this: chaos! If I got a second word, it would be: disaster.

Eight agencies oversee the government’s food-related policies, and they largely work in silos. They rarely coordinate with one another to achieve a common goal, which makes their policies confused and conflicted. In many cases, they directly contradict one another.

On top of that, most of our food and agriculture policies undermine public health, harm the environment, and increase private profits.

LE: How is the government subsidizing this problem?

Dr. Hyman: Some of the most heavily subsidized foods, like corn and soybeans, are plants that are not inherently unhealthy. But the vast majority of these crops are not consumed whole.

Only **1%** of American-grown corn is sold and eaten whole as corn on the cob. Much of the rest is either fed to factory-farmed livestock to fatten them up before slaughter or converted into biofuels.

As for what does hit your plate, America’s heavily subsidized bounty of corn and soy may start out as whole foods, but by the time you eat them, they’ve been manufactured into ultraprocesed oils and sweeteners and food additives.

Even worse: If those farmers want to diversify and grow tomatoes and broccoli on their farms, they lose all their government support.

As a result of farm subsidies, taxpayers are footing the bill for the chronic disease epidemic while simultaneously underwriting the production of the very foods that are causing it.

LE: Food is the problem...but it’s also the solution.

Dr. Hyman: The reason this problem is pretty much ignored or attacked piecemeal is that this epidemic has come on fast and furiously over the last 40 years and blindsided society and governments. And better medication or medical care can’t solve these chronic diseases.

The solution? Our forks.

Mounting research proves that food is medicine and demonstrates how whole foods, especially an increase in vegetables and fruit, can prevent or reverse chronic disease.

At Geisinger Health Systems, providing food-insecure poorly controlled type II diabetics with a year's worth of whole foods reduced health care costs by **80%** and dramatically improved their health outcomes.

According to Dr. Dariush Mozaffarian, "The idea of food as medicine is not only an idea whose time has come. It's an idea that's absolutely essential to our health care system."

LE: Let's switch gears and talk about the environmental impact of our current food system. How are current farming practices harming the planet—and threatening our future?

Dr. Hyman: Our food system isn't just making the world's population sick; it's making the environment sick. Innovations in agriculture over the last century have allowed us to produce more food than ever, but at a serious cost.

The methods we use to grow food are contributing to our future inability to grow food, by increasing

greenhouse gas emissions, raising temperatures, and making current cropland unfarmable.

The U.N. projects that in 60 years we may completely "mine" all our topsoil, making it almost impossible to grow food. Soil gone. No food. No people. That's 60 more harvests.

What will your grandchildren eat?

Water scarcity is also a huge issue; at the World Economic Forum, I heard Jim Kim, the former head of the World Bank, say, "The wars of the future will be fought over water, not oil."

Through tillage and erosion, soils have lost 133 billion tons of carbon into the atmosphere since we started farming, driving global warming.

Big fertilizer conglomerates produce 20 million metric tons of fertilizer a year using fossil-fuel-intensive processes. When that fertilizer is applied to farms, the damage is wrought on the soil, and it weakens plants, pollutes water systems, and drives huge external costs.

Halting land degradation has become an urgent global imperative.

LE: How could regenerative agriculture help solve the water shortage problem?

Dr. Hyman: Water is a limited resource. Only **5%** of water on the planet is fresh water. We are depleting our ancient aquifers faster than rainfall can replenish them.

The biggest one in America, the Ogallala Aquifer in the Midwest, is being depleted by more than a trillion gallons more a year than can be refilled by rain. Irrigation of crops is the main cause.

Dirt can't hold water. Soil can. If we switched to range (grass)-fed regenerative livestock production, we would restore soils, draw down carbon (reversing climate change), and store massive amounts of water, which can prevent floods and droughts.

LE: What could be done politically to change this destructive system?

Dr. Hyman: For starters, the government has to reform its subsidies system. Farmers need incentives to





FOR MORE INFORMATION

For a quick reference guide to all the solutions outlined in *Food Fix*, visit www.foodfixbook.com. To learn more about any of the issues that stem from our food industry, take a look at the online resource guide for articles, studies, reports, books, videos, companies, and organizations that are raising awareness and changing the conversation at www.foodfixbook.com/resources.

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grow more nutritious foods using regenerative practices.

Subsidies should also support farmers to transition to organically or regeneratively grown crops, grass-fed and grass-finished pasture-raised livestock, and organically produced milk. These subsidies can help farmers buy new seeds, develop new crops, and purchase new farm equipment that will help them transition to more regenerative practices.

Beyond subsidies, the federal government feeds millions of people in schools, hospitals, and prisons, as well as military and government workers.

It can promote healthy eating and create markets for farmers by requiring that schools, prisons, and military bases use a percentage of their budgets to buy locally sourced food from nearby farms and, at the very least, healthy whole foods that promote health rather than disease.

A national food policy would transform our broken food system into one that aligns public health objectives with economic and

environmental goals. It would make healthful choices the default option for Americans while slashing health care costs and helping farmers, protecting the environment, and reversing climate change.

LE: How can individuals advocate for change?

Dr. Hyman: These are just a few of the many innovations and ideas moving from the margins to the center and providing a road map for fixing our food system.

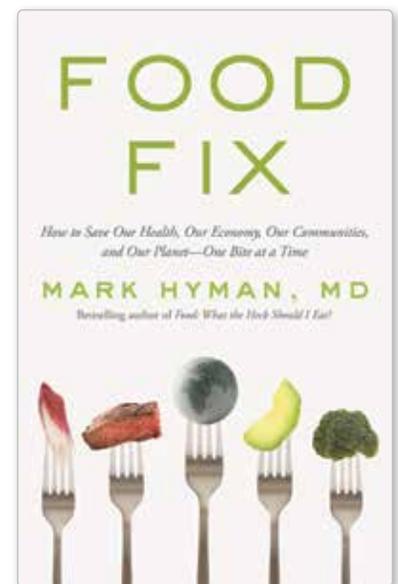
It is the great work of our time. And it depends on all of us.

We need a national (and ultimately global) campaign to fix our food system. If you're interested in helping transform our food system and want to learn more, please join our campaign and prescription for a new food system at www.foodfix.org. •

ABOUT THE AUTHOR:

Mark Hyman, MD is the Head of Strategy and Innovation for the Cleveland Clinic Center for Functional Medicine, and founder and director of The UltraWellness Center. He is the bestselling author of numerous books, including, *Food: What the Heck Should I Cook?; Eat Fat, Get Thin; and The Blood Sugar Solution 10-Day Detox Diet*.

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3. **Cyanidin-3-glucoside** to assist with night vision.⁶⁻⁸
4. **Astaxanthin** for comprehensive eye health support and to fight eye fatigue.⁹
5. **Saffron** to help support vision, based on study subjects seeing an average of two additional lines on an eye chart used by doctors to test vision.¹



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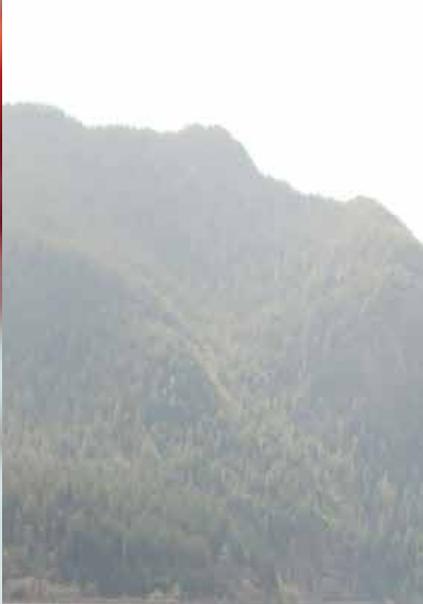
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Restore Youthful Cell Function via AUTOPHAGY

BY CELIA SIMMONS



With age, the insides of our cells accumulate damaged proteins and other debris that impair youthful function.

Humans are equipped with a built-in process that removes these toxic waste products to make room for healthy internal regeneration.

This natural, cell housekeeping process is called **autophagy**.

Autophagy *declines* with age and poor diet,¹ causing cells to be damaged at an increasing rate.²

Animal studies show that *stimulating* **autophagy** leads to improvements in healthspan and **increased longevity**.³⁻⁵

Scientists at **Life Extension**[®], in collaboration with the **Insilico Medicine** research group, identified two plant extracts that stimulate **autophagy**.

What Is Autophagy?

Every cell in the body contains **proteins** and other components that serve vital metabolic purposes, from regulating cellular function to facilitating biochemical reactions.

When we are young, our internal cell machinery and its built-in cleaning process (autophagy) work at peak efficiency. This enables younger cells to clean up their metabolic waste.

The literal definition of autophagy is **self-eating**. In this process, the cell consumes and breaks down old cellular parts and debris.

This normal autophagy process supports healthy tissue function and **promotes overall health**.

But aging and poor diet contribute to *lower* rates of autophagy.^{1,4}

As autophagy slows down, metabolic waste products and toxins accumulate. This slowdown compromises optimal cellular function.

The result is that cell health and function rapidly *decline*. This autophagy decline has been linked to many diseases of older age.^{4,6-10}

Boosting Autophagy Extends Healthy Lifespan

In recent years, scientists investigating ways to maximize lifespan and reduce risk of chronic disease have increasingly focused on **autophagy**.^{4,6-9}

In several animal studies, *stimulating* autophagy led to **increased longevity**.³⁻⁵

One study activated **autophagy** in mice by altering gene expression. The **lifespan** of these mice was extended by an average of **17.2%**.⁵

This would be the equivalent of increasing the **average human lifespan** in the U.S. from **78.5 years** to **92 years**.

These animals didn't just live longer. They were also healthier.

They maintained **lower body weight** than normal mice well into older age. They had increased insulin sensitivity, indicating improved metabolic health. And they had better physical functioning.

When the scientists *inhibited* the **autophagy** process, all these beneficial effects disappeared. That indicates that autophagy stimulation was the factor responsible for the health and longevity improvements.





Ways to Stimulate Autophagy

Research has shown that during times of **intermittent fasting** or **caloric restriction**, when nutrients are scarce, cells activate **autophagy** on their own.^{11,12}

Physical **exercise** also stimulates autophagy.¹³

At a cellular level, two regulatory proteins play a key role in controlling autophagy: **mTOR** and **AMPK**.

The protein **mTOR** acts as a nutrient sensor. When **caloric intake** is high and nutrients are abundant, mTOR is activated and **shuts off** autophagy.¹⁴ Inhibiting excess **mTOR activity**, on the other hand, can lead to **increased autophagy** (removal of cellular waste).

Said differently, constant consumption of **calories** denies aging cells the ability of clean house via **autophagy**. Fasting **16-18 hours** most days can facilitate autophagy, but most people need ancillary support in the form of drugs or nutrients that suppress excess **mTOR**.

AMPK is an **activator** of autophagy. Stimulating AMPK has been shown to improve metabolic health and lifespan.¹⁴⁻¹⁶

Using this knowledge, scientists set out to discover effective ways to stimulate autophagy.

WHAT YOU NEED TO KNOW

Keep Cells Working Smoothly

- Autophagy is a process cells use to remove old and damaged parts and replace them with new ones. This helps keep cells clear of debris, youthful, and fully functional.
- With age comes a decrease in autophagy, combined with an increase in accumulated damage, accelerating the aging process and increasing risk for many chronic diseases.
- Scientists have identified two nutrients that can stimulate autophagy: the flavonoid luteolin and piperlongumine, a compound isolated from the long pepper plant.
- Working in overlapping and distinct ways, these nutrients can help to maintain cells clear of debris, and functioning to promote better health.



Autophagy Enhancers and Senolytics: A Powerful Pair

Cellular **senescence** is a major contributor to the aging process. Senescent cells have become old and dysfunctional but refuse to die off to make room for new, healthy cells.

Compounds called **senolytics** can *remove* these harmful cells from tissues.

One effective senolytic approach is a weekly combination of **quercetin**, **theaflavins**, and **apigenin**, together with the recently *bioavailable* **fisetin**.

Using senolytics *and* nutrients that activate **autophagy** is a way to help fight aging.

Autophagy helps to keep cells healthy and potentially functioning longer, while **senolytics** get rid of cells that are *already* damaged.

These interventions may help keep tissues in peak form and prevent age-related deterioration and disease.

Working with advanced **artificial intelligence (AI) technology**, they focused on two nutrients, **luteolin** and **piperlongumine**.

Each has been shown to induce **autophagy** individually via overlapping and distinct mechanisms.

Luteolin Protects Brain and Body

Luteolin belongs to the **flavonoid** group of plant nutrients. It is found in several fruits, vegetables, and herbs, including broccoli, parsley, and thyme.

Luteolin has been shown to both **increase AMPK** activity and **inhibit mTOR** signaling.¹⁷⁻²⁰ The cumulative effect is that **autophagy** is activated, and cellular metabolism is improved.

In animals and cell culture, treatment with **luteolin** has been shown to protect the brain, heart, and tested cells.²¹⁻²⁹

For example, animals with a **brain injury** fared better than their non-treated counterparts when given **luteolin**.²⁷

Autophagy was activated, inflammation was reduced, and the overall outcome and recovery from the injury were improved.

Piperlongumine Keeps Cells Youthful

Piperlongumine is a compound isolated from the **long pepper** plant.

Like luteolin, piperlongumine has been shown in animal and cell-culture studies to **activate autophagy** by inhibiting mTOR signaling.^{30,31} There is also evidence that it activates AMPK.³²

But piperlongumine encourages autophagy in another way that's distinct from luteolin.

A protein known as **beclin-1** is a critical *activator* of **autophagy**. Another protein, called **Bcl-2**, binds to beclin-1 and *blocks* its ability to start autophagy.

Piperlongumine causes the release of **beclin-1** from Bcl-2, allowing it to *activate* autophagy.³⁰

Luteolin and piperlongumine hold promise in maximizing healthy autophagy, rejuvenating cells, and maintaining their optimal function.

Summary

Autophagy declines with age and poor diet, causing cells to become overwhelmed by damage and metabolic waste at an increasing rate. This leads to accelerated aging and increased risk for **chronic disease**.

Stimulating autophagy can help prevent this slide into old age, improving the health and extending the lifespan of animals.

Scientists at the **Insilico Medicine** group in collaboration with LifeExtension® have found two nutrients that activate autophagy: **luteolin** and **piperlongumine**.

In overlapping and distinct ways, they stimulate beneficial autophagy. Together, they can help keep cells functioning youthfully for improved health. •

What is Insilico Medicine?

Discovery of new medicines and nutraceuticals often takes years. Insilico Medicine has created a paradigm shift by using advanced **artificial intelligence** that reduces development time and costs by analyzing thousands of data points to identify nutrients that reduce aging factors.

With over 120 scientists, the Insilico Medicine group uses **deep-learning artificial intelligence technology** to identify compounds to circumvent deleterious aging processes.

A unique aspect of Insilico's research into dietary ingredients is referred to as "geroprotectors" that mimic the young, healthy signaling state in older human tissues. This research has allowed Insilico to identify nutrients that target aging factors such as **cellular senescence**, declining **stem cell health** and reduced **autophagy**. These nutrient-based "geroprotectors" provide research-driven data to create formulations that foster longevity and increased lifespan.

In addition to nutrient discovery, Insilico works with global pharma and biotech to discover new therapeutics to treat cancer, immune dysfunction and senescence



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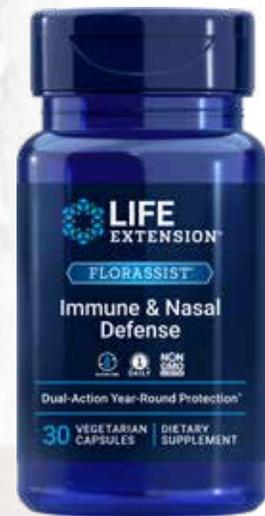
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40 vegetarian chewable tablets

5-Day Regimen: Rapid, Go-To Support for Healthy Immune Response



Immune challenges can hamper your day. We added zinc to our standardized elderberry extract and vitamin C formula to encourage an immediate immune response. Our berry-flavored tablet packs intense nutritional support designed to call up your body's immune defenses when you need them most. Take eight tablets a day for five days to promote a healthy immune response and help you stay at your best.

NEW PRODUCTS



Clinically Studied Dose of Vitamin K2 for Healthy Bones



Maintaining your bone health is essential for quality of life. Vitamin K2 is vital for osteoblasts' normal activity, specialized cells that regulate bone mineralization. This process binds calcium ions and deposits them into the bone. Studies show you need about 45,000 mcg of this special kind of vitamin K2 to get the maximum benefits. And that's the exact dosage in our bone-friendly formula!

Item #02417 • 30 capsules

Give Your Body's "Cellular Housekeeping" Process a Nudge



Your body clears cellular debris to help keep you vibrant and healthy, a process known as autophagy. Unfortunately, this process begins to decline over time.

The right nutrients help boost your body's autophagy process. That's why we combined plant flavonoid, luteolin, and an alkaloid from pepper called piperlongumine to support your body's healthy cleanup process, and with it, longevity.

Item #02415 • 30 vegetarian capsules

Sometimes, "Dense" is More Encouraging Healthy Bone Density



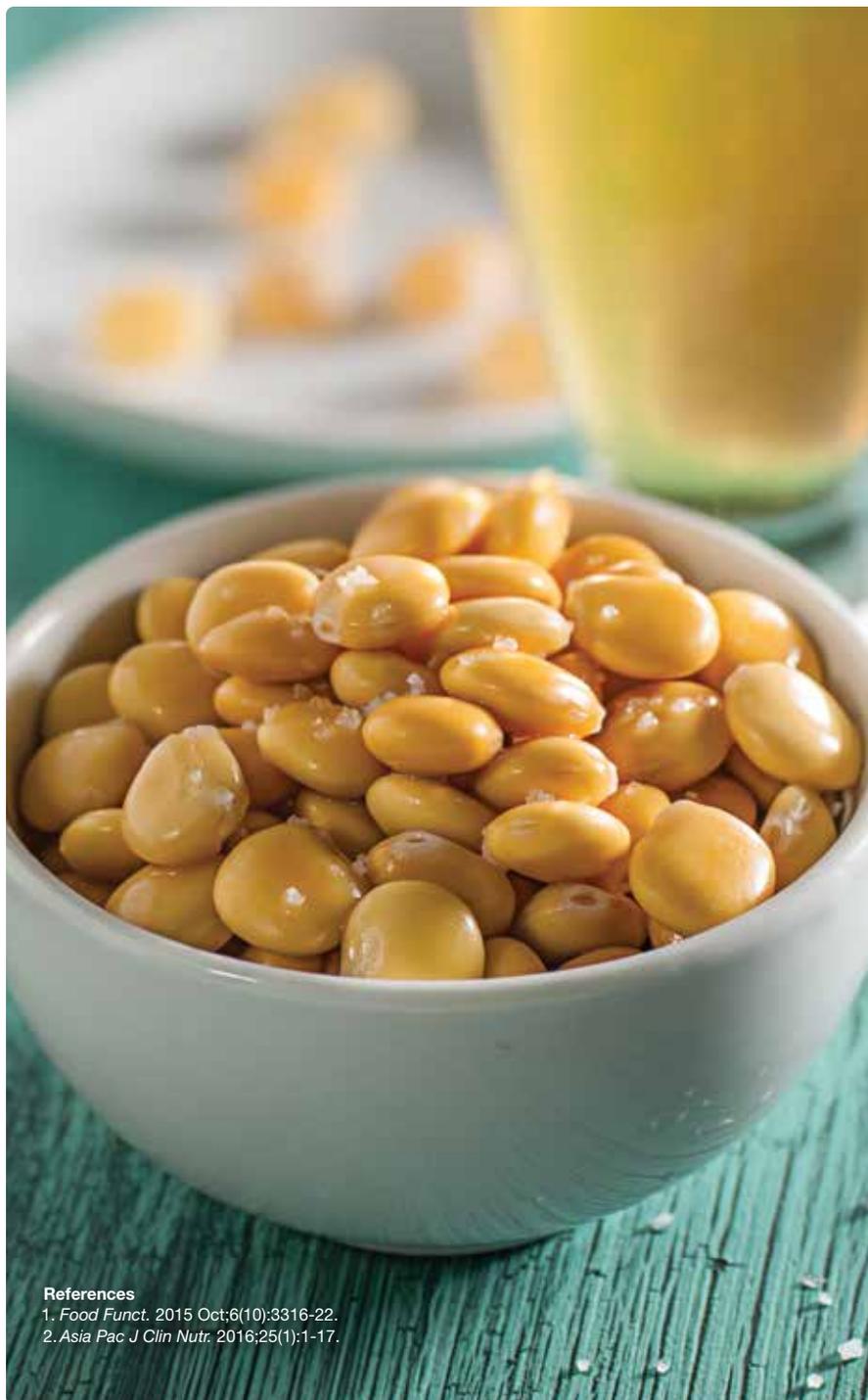
Item #02416 • 120 capsules

Your body's process for maintaining healthy bone density declines over time. Studies show that a special form of vitamin K2, known as menaquinone-4, is especially effective at encouraging healthy bone density. Our multi-ingredient formula delivers optimal bone density support with 45 mg of vitamin K2, easily absorbed calcium and essential bone-friendly nutrients such as magnesium and boron.



Lupini Beans

BY LAURIE MATHENA



References

1. *Food Funct.* 2015 Oct;6(10):3316-22.
2. *Asia Pac J Clin Nutr.* 2016;25(1):1-17.

Lupini beans are a common snack in Mediterranean regions, dating back as far as 4,200 years. But they've only made an appearance in the U.S. in recent years.

Raw lupini beans are a protein powerhouse ready to meet the growing demand for plant-based protein sources.

Lupini beans (also called *lupin* beans) provide **more** protein than chickpeas, **fewer** carbs than pistachios, and **fewer** calories than almonds.

They also have more fiber than chickpeas, oats, and quinoa.

Lupini beans contain very little starch or sugar, making them an ideal low-carb option for type II diabetics or anyone else concerned about keeping their blood sugar balanced.

An in-vitro study found that lupini beans increase the generation of short-chain fatty acids in the gut, while also increasing the population of good gut bacteria.¹

Numerous randomized, controlled clinical trials have shown that replacing meat with legumes like lupini beans has a positive impact on longevity, diabetes, cardiovascular disease, and weight management.²

Eating lupini beans may also lower blood pressure, improve blood lipids, and improve insulin sensitivity.²

Consumed whole, lupini beans can be added to salads or combined with roasted vegetables.

When they're ground up, these beans have a neutral taste, making them a versatile dish that can take on the flavor of any spices for which you're in the mood. They also provide a low-carb option to quinoa or rice.



Item #02497
60 softgels

Triple Protection for Your Ticker.

Your heart keeps the beat for your entire body. Hidden inside your arteries and veins is the vascular endothelium—a thin layer of cells that keeps your system running like clockwork.

Endothelial Defense™ Pomegranate Plus keeps your cardiovascular gears turning with pomegranate, melon extract and more.

Pomegranate—protects arteries from oxidation with free-radical-quenching polyphenols.

Extramel® melon concentrate—encourages production of superoxide dismutase, a naturally occurring antioxidant.

Cardiose®—promotes circulatory health with hesperetin extracted from sweet orange peels.

This product is available at fine health food stores everywhere.

Cardiose® is a registered trademark of INTERQUIM, S.A. d.b.a. Ferrer HealthTech. Extramel® is a registered trademark of Bionov.

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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