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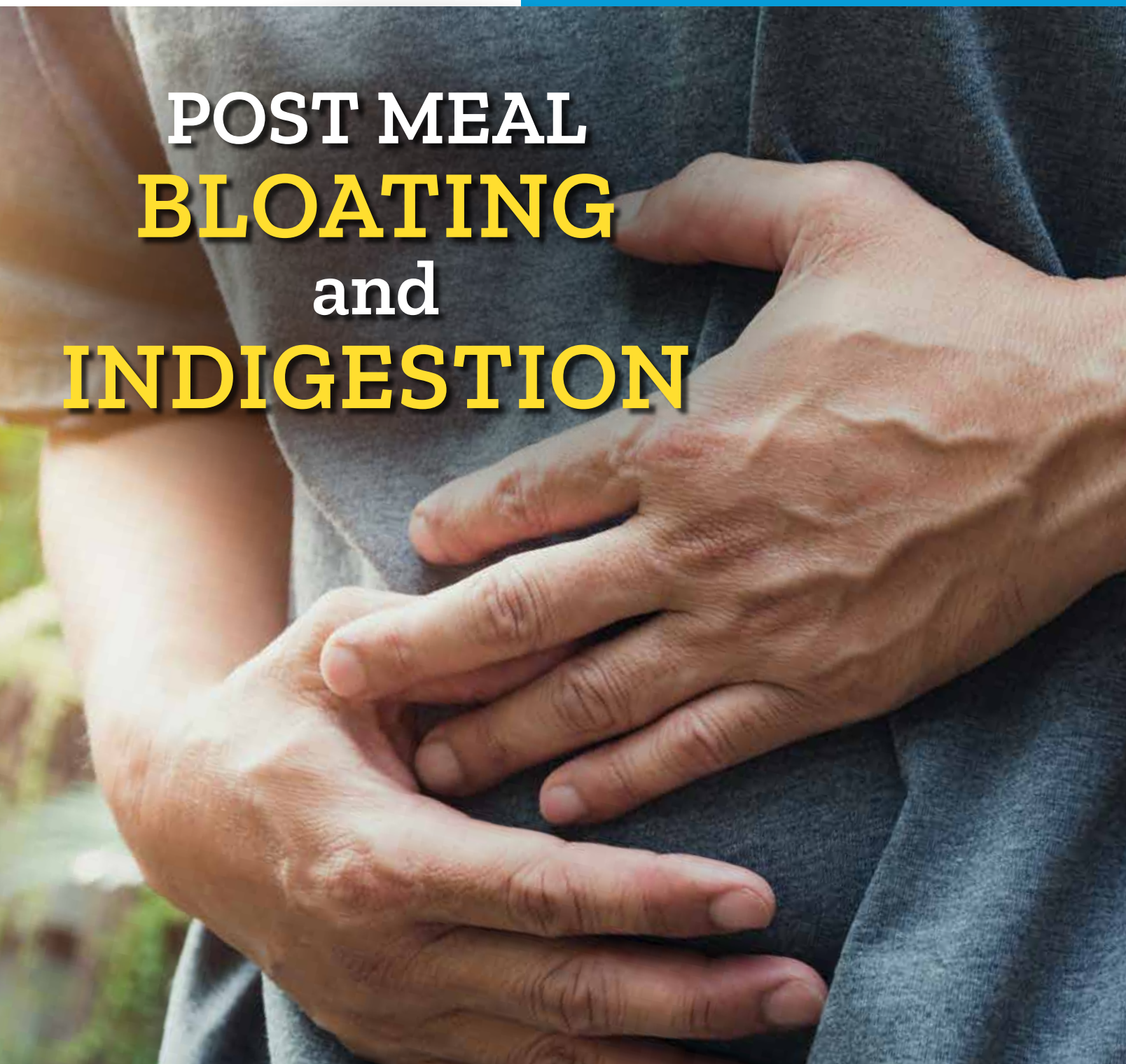

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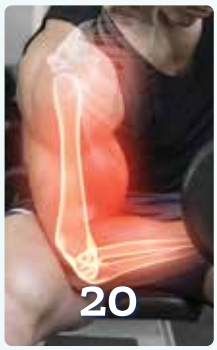


Enhancing the Health Benefits of FISH OIL

BY MICHAEL DOWNEY

The benefits of the **Mediterranean diet** are well established.

They include reduced **cardiovascular** and **neurological** risks along with lower overall **mortality**.[1-7]

Components of the Mediterranean diet are comprised of fish, olive oil, nuts and seeds, vegetables and fruits, and whole grains.

Science today enables people to receive many **Mediterranean diet** components using concentrated:

- **Fish oil rich in EPA/DHA**
- **Olive fruit and leaf extract**
- **Sesame seed lignan extract**

To conveniently deliver these nutrients, researchers have combined **fish oil**, **olive polyphenols**, and **sesame lignans** to enhance overall health benefits.

The **omega-3 fatty acids** found in **fish oil** have a wide range of benefits for human health and longevity.

Populations that consume large amounts of oily fish have *reduced* incidence of **cardiovascular disorders**, which include heart attacks, hypertension, strokes, atrial fibrillation, and heart failure.[8-11]

A meta-analysis found that the *highest* consumption of the omega-3s **EPA** and **DHA** is associated with a **14% reduction** in the risk of dying from *any* cause, compared to the lowest omega-3 consumption.[12]

In the analysis, each additional **200 mg** of **fish oil** consumed per day led to a **7% reduction** in the overall risk of death.[12]

Fish oil works in many different ways to achieve these benefits.

It helps lower levels of **triglycerides**, fats linked to risk of heart disease. It reduces the buildup of plaque on artery walls that restricts blood flow, and improves function of the **endothelial cells** that line blood vessels.[8,9]

Fish oil also combats **chronic inflammation**, which plays a key role in age-related disease.[13,14] That helps prevent:[15-23]

- Metabolic disorders, such as obesity and diabetes,
- Cancer,
- Neurological disorders, such as depression and Alzheimer's,
- Autoimmune diseases,
- Chronic kidney disease, and
- Non-alcoholic fatty liver disease (NAFLD).

Olive Extract

Olive oil has long been considered a crucial contributor to the Mediterranean diet's benefits.[24]

Research shows that people who consume the most olive oil have a lower risk of dying from **cardiovascular** events, **strokes**, or ***any cause at all,*** compared to those who consume the least.[25]

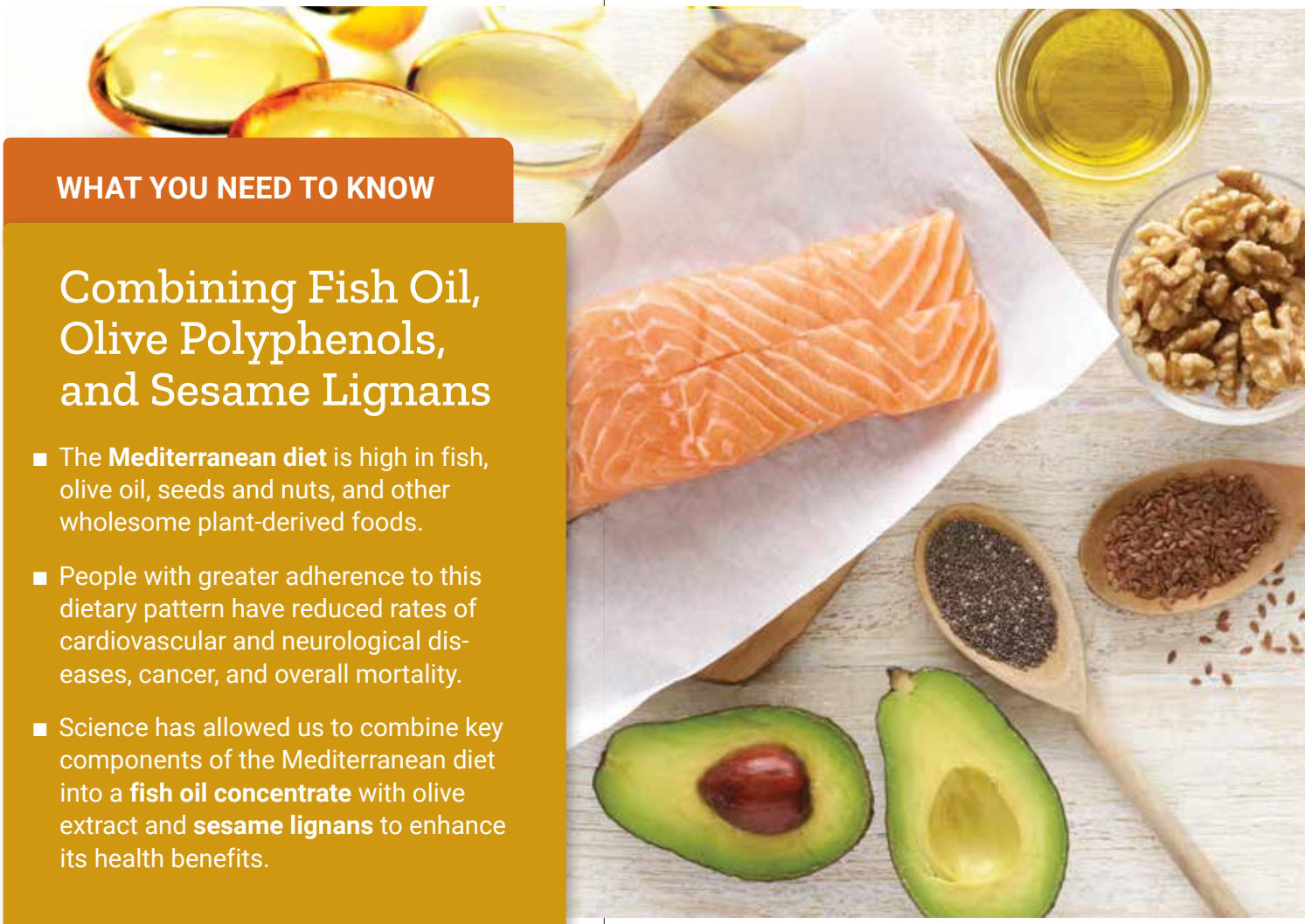
Consuming olive oil daily may also protect against conditions ranging from Alzheimer's and osteoporosis to skin aging and cancer.[26-29]

Polyphenols are beneficial components present in olive oil that include **oleuropein**, **tyrosol**, and **hydroxytyrosol**.[30-32]

Hydroxytyrosol is one of the most common polyphenols present in **extra virgin** olive oil.[31] In people over age 65, those who ingest the *highest* amount of **hydroxytyrosol** have been shown to live, on average, **9.5 years longer**.[33]

Extracts of the **olive leaf**, concentrated and standardized to provide maximum polyphenol content, have been shown to protect cultured heart-muscle cells from destruction caused by **oxidative damage**.[34] In a study in aged rats, olive polyphenols decreased stress-induced tissue damage and boosted intracellular resistance systems.[35]

In a rat model of **metabolic syndrome**, olive extracts *improved* or normalized accumulation of **fat** in the abdomen and liver, excessive collagen deposits in the heart and liver, cardiac stiffness, poor glucose tolerance, and abnormal lipid profiles.[36]



WHAT YOU NEED TO KNOW

Combining Fish Oil, Olive Polyphenols, and Sesame Lignans

- The **Mediterranean diet** is high in fish, olive oil, seeds and nuts, and other wholesome plant-derived foods.
- People with greater adherence to this dietary pattern have reduced rates of cardiovascular and neurological diseases, cancer, and overall mortality.
- Science has allowed us to combine key components of the Mediterranean diet into a **fish oil concentrate** with olive extract and **sesame lignans** to enhance its health benefits.

Unique Power of Sesame Seeds

Sesame seeds have long been a component of the Mediterranean diet,[37] whether added to dishes or ground into tahini or hummus.

They contain high concentrations of polyphenols called **lignans**. They may reduce blood lipid levels, fight inflammation and cancer, neutralize free radicals, and enhance **vitamin E** bioavailability (absorbability).[38,39]

Metabolism of **sesame lignans** by intestinal microflora creates *other* compounds, enterolactone and enterodiol, both of which may have protective effects against **hormone-related diseases** such as breast cancer.[40,41]

Sesame lignans may help enhance the effects of **omega-3s** in the body, making them a complement to add to fish meals and fish oil supplements.

Summary

People who follow a **Mediterranean diet**, typically rich in fish and olive oil, have lower risk of cardiovascular disease, neurological disorders, cancer, bone loss, and overall mortality.

Research indicates that **fish oil** rich in omega-3 fatty acids offers anti-inflammatory and disease-prevention benefits.

Based on the impressive findings about the Mediterranean diet, combining **fish oil concentrate** with **olive extract** and **sesame lignans** may enhance overall health benefits. •

Omega-3 Supplementation Reduces Cardiovascular Disease Death

The ***Mayo Clinic Proceedings*** recently published a meta-analysis showing that omega-3 supplementation is associated with significant reductions in the risk for cardiovascular disease death.[42]

The study looked at 40 clinical trials and concluded that supplementation with **EPA** and **DHA** reduced risk of coronary heart disease, including heart attack.

Specifically, the study found that EPA+DHA supplementation is associated with a **reduced risk** of:

- Fatal myocardial infarction (**35%**)
- Myocardial infarction (**13%**)
- Coronary heart disease events (**10%**)
- Coronary heart disease mortality (**9%**)

The cardiovascular protection was greater with *increases* in omega-3 dosage.

Increasing intake of EPA and DHA by **1,000 mg** per day was associated with a ***reduction*** of **5.8%** in the risk of cardiovascular disease events.

Robust evidence suggests benefits from daily supplementation with EPA+DHA.

Today's fish oil products deliver a higher content of EPA/DHA per serving. Aging adults should consider taking at least **1,400 mg** of EPA and **1,000 mg** of DHA daily with meals that contain some fat to facilitate **absorption**.

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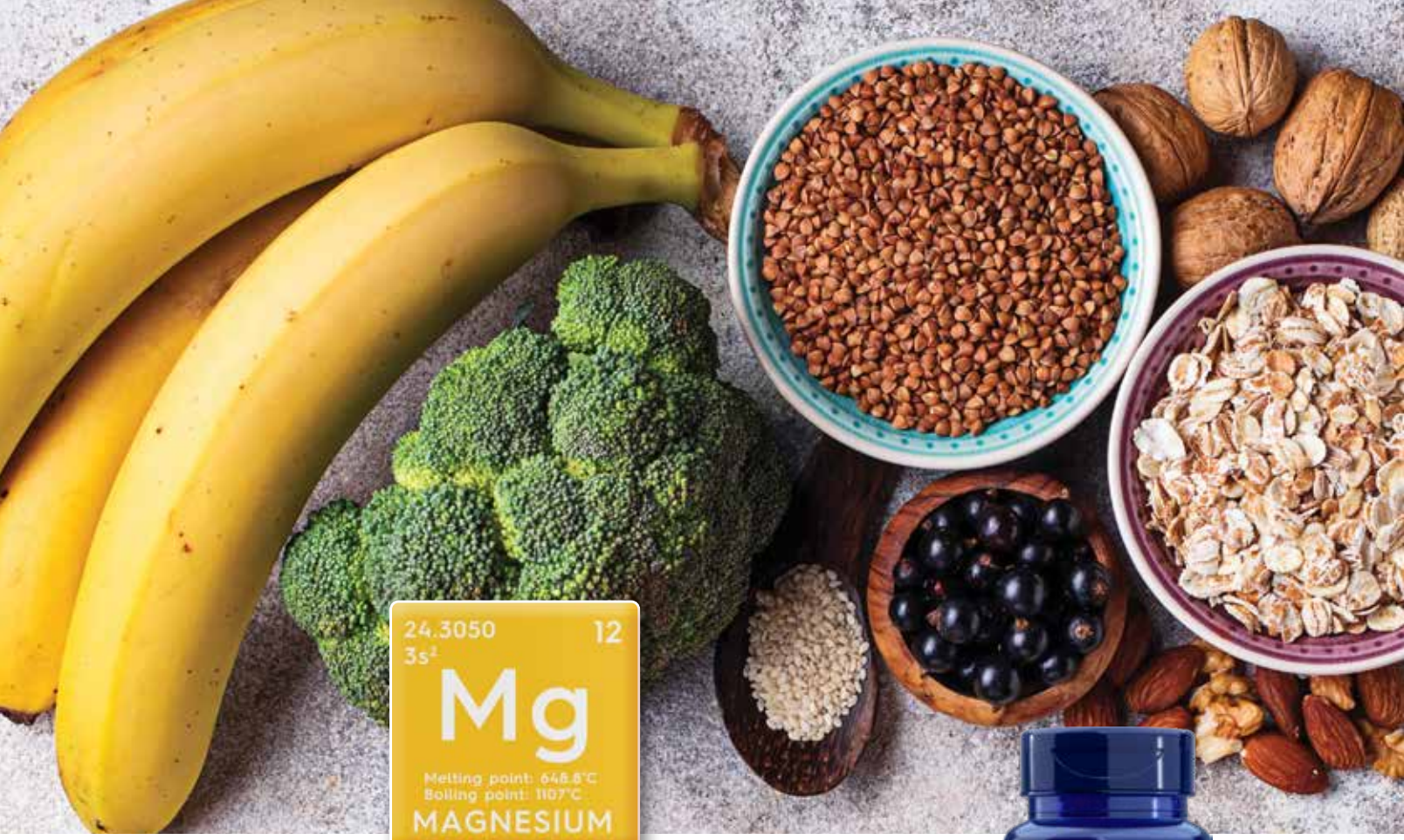

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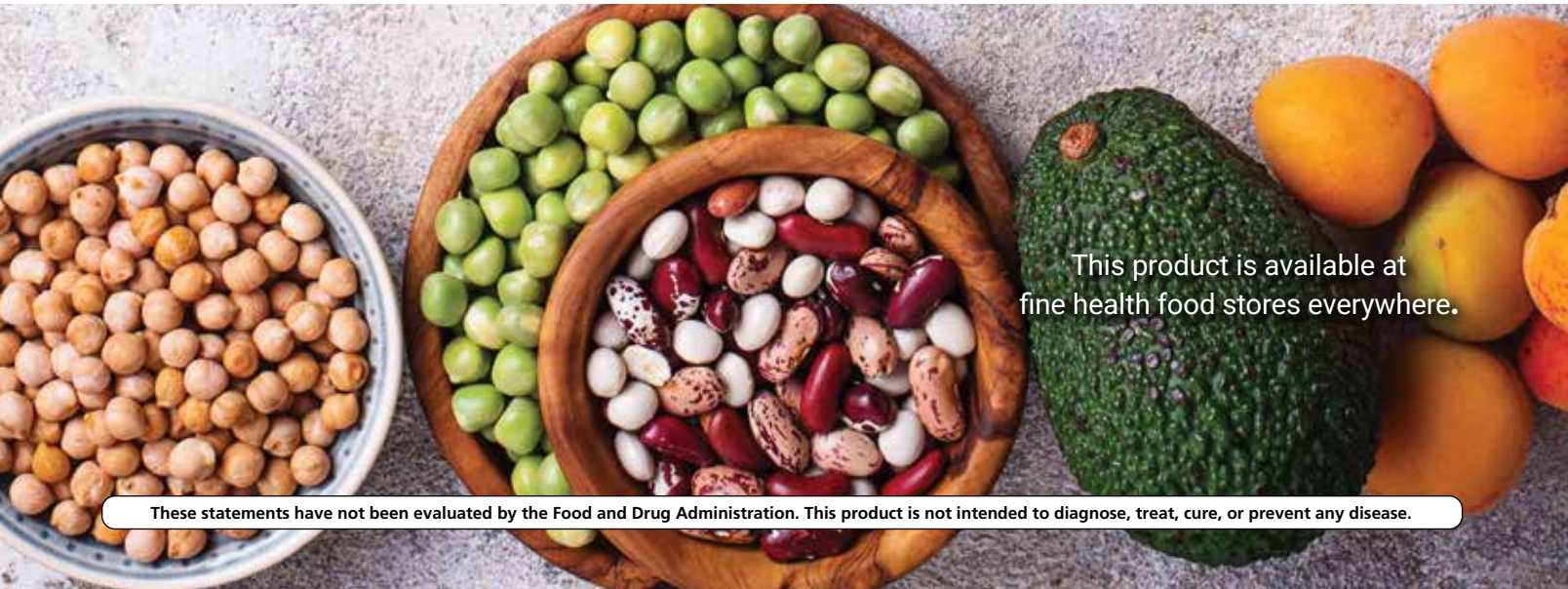

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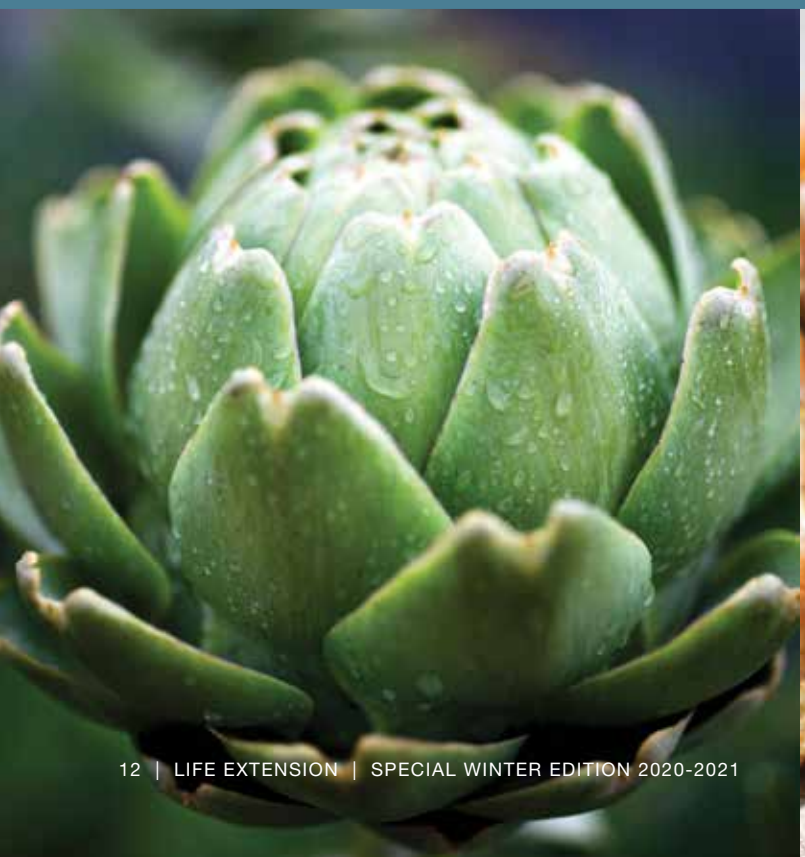
Thwart **POST-MEAL** Bloating and Indigestion

BY MICHAEL DOWNEY



As people age, they often experience bloating, gas, or nausea before they even finish a meal.

It's more common than most people realize.

Up to **30%** of people suffer from after-meal **bloating**, that uncomfortable feeling that your belly is swollen.[1-3]

Even when small meals are consumed, after-meal **bloating** remains a widespread problem.

Scientists have identified four **plant extracts** that target ***underlying causes*** of gastrointestinal discomforts.

In one human trial, more than **63%** of the subjects taking an **artichoke-ginger** blend experienced significantly reduced feelings of bloating, gassiness, nausea, and other symptoms of indigestion.[4]

A **fennel-curcumin combination** relieved symptoms of **irritable bowel syndrome**, including bloating and stomach pain, by more than **50%**, and ***completely prevented all symptoms*** in **25.9%** of users.[5]

Taken together, these nutrients promise to relieve post-meal distress and improve quality of life.

The Causes of Bloating

Bloating is one of the most commonly reported gastrointestinal symptoms. It's characterized by a feeling of excessive fullness, trapped gas, distension, and abdominal pressure and pain.[2]

No treatment has proven consistently effective,[2] and drugs may have serious side effects.

Propulsid® was a drug frequently prescribed to alleviate bloating. But it *caused* abdominal pain, indigestion, gas, and nausea.[6] It was removed from the U.S. market after it was associated with heart rhythm abnormalities.[7]

Two of the **underlying causes** of after-meal bloating are slow **gastric motility** and excess **gas production**.

When **gastric motility** slows, the ability of the stomach muscles to move food through the digestive tract is impaired.

Artichoke and Ginger

Indigestion in the upper abdominal region is described as bloating or gassiness, a burning sensation, nausea, or feeling too full too quickly after starting to eat.

About **40%** of patients have abnormally **delayed gastric emptying**, which means food simply sits in the stomach longer than it should.

Prokinetic drugs *accelerate* gastric emptying. They are often used to treat indigestion. But like Propulsid®, they have side effects.[8]

Fortunately, there are specific **nutrients** used for centuries that safely facilitate **gastric emptying**.

Researchers first focused on **artichoke leaf** and **ginger root**, which have long been used in traditional medicine to treat indigestion.[8-10]

Ginger has been shown in animal and human studies to promote **gastric motility**.[4,8,10]

Artichoke promotes **bile acid** secretion from the liver. Bile acid secretion is essential for *accelerating* gastrointestinal transit.

Artichoke is also an **antispasmodic**, which means it suppresses gut spasms or cramping. This also helps speed the movement of food through the digestive tract.[4,8,10]

Scientists decided to combine **ginger** and **artichoke extracts** to test their effects on bloating.[4,11]

Human Trials

Researchers created a blend of **100 mg** of a**rtichoke leaf extract** and **20 mg** of **ginger root extract**.[4,11]

They tested it on 126 healthy men and women, aged 18-70, who had **functional dyspepsia** (indigestion).

This was defined as having had complaints of *early* satiety (fullness), postprandial fullness (feeling *too* full after eating), bloating, or nausea for at least three months during the last year, without a known structural or biochemical cause.[4]

In a randomized, double-blind, placebo-controlled study, two groups took either **120 mg** of the **artichoke-ginger blend** or a **placebo** twice daily. Patients rated the severity of each of six dyspeptic symptoms: fullness, bloating, early satiety, nausea, vomiting, and upper abdominal pain.

In 14 days, **44.6%** of participants taking the **artichoke-ginger blend** had a marked (clinically significant) **improvement** in digestive symptoms, compared to **13.1%** of the placebo users.

After **four weeks**, **63.1%** of the **artichoke-ginger** group had a **marked** symptom improvement, while only **24.6%** showed improvement in the **placebo** group. No adverse effects were reported.[4]

In another study, scientists used ultrasound to measure the size of the stomach area of 11 healthy men and women, aged 20-60, both before and after a standardized meal.[11]

When the **artichoke-ginger blend** was taken, subjects had a significantly *smaller* stomach area than when the placebo was taken. This indicates that the **artichoke-ginger** blend works by encouraging ***enhanced gastric emptying***.[11]

Fennel Seed and Curcumin Relieve Pain and Gas

Two other nutrients have been used to aid digestion: **fennel** and **curcumin**.

Seeds from **fennel**, a plant known for its licorice flavor, have long been consumed after meals to promote digestion and prevent flatulence.[12]

Studies show that fennel **reduces gas production** by inhibiting the activity of a methane-producing bacterial enzyme.[13]

In addition, clinical trials have shown that fennel seeds, tea, and seed oil promote **gastrointestinal stimulation**, improving gastric motility.[5,14,15]

Like artichoke, fennel also has an **antispasmodic** effect, reducing irregular muscle contractions that impair normal gut motility.[5]

Researchers combined fennel seed oil and a low-dose curcumin in a clinical trial to test their effect on bloating and abdominal pain.[5]

Clinically Effective

Scientists enlisted 121 male and female volunteers, aged 18-60, who suffered from **irritable bowel syndrome** (IBS) for a randomized, double-blind, placebo-controlled trial.[5] IBS is a chronic disorder characterized by abdominal pain, bloating, and abnormal bowel movements in the absence of identifiable cause.

Participants took a capsule twice daily that contained either a placebo or a combination of **25 mg** of **fennel seed oil** and **42 mg** of **curcumin**.

WHAT YOU NEED TO KNOW

Relief for Post-Meal Problems

- **Bloating** is one of the most common gastrointestinal symptoms, marked by a feeling of excessive fullness, gas, and abdominal pressure and pain.
- Scientists have identified **four clinically effective** compounds that target the ***underlying causes*** of bloating before it occurs.
- A blend of **artichoke leaf** and **ginger root** extracts relieves symptoms of **dyspepsia** (indigestion), including bloating, nausea, vomiting, and upper abdominal pain.
- A mix of **fennel seed oil** and curcumin decreases bloating, abdominal pain, and other severe symptoms of **irritable bowel syndrome**.
- Taken together, **ginger root**, **artichoke leaf**, **fennel seed oil**, and **curcumin** may help prevent or significantly reduce gastrointestinal distress, and improve quality of life.

Researchers **combined** low-dose curcumin with fennel seed oil to reduce assorted symptoms of bloating. The curcumin was added to reduce inflammation in the gut. Fennel seed oil was used for its antispasmodic properties.

When these two compounds were used **together**, researchers found reduced abdominal pain and abdominal distention in study subjects.

After 30 days, those taking the **fennel-curcumin** mix reported an average **50.05%** decrease in bloating, abdominal pain, and other IBS symptoms, nearly double the **26.12%** decrease in the **placebo** group.[5]

All symptoms were improved by treatment. Among those taking the **fennel-curcumin** mix, **25.9%** became ***completely symptom-free***, compared to **6.8%** of **placebo** users.

The treated group also reported significant improvement in quality of life, with no adverse effects.

Taken together with **ginger root** and **artichoke leaf**, this **fennel-curcumin** combination may significantly improve or even *prevent* after-meal bloating, gas, and abdominal pain, providing a solution to a problem many people thought they just had to live with.

Summary

Up to **30%** of people complain of **bloating** after eating, which is often accompanied by gas, abdominal pressure and pain, and reduced quality of life.

Scientists have identified four compounds that target the underlying causes of this discomfort, which are slow **gastrointestinal motility** (movement) and excess **gas production**.

Ginger root, **artichoke leaf**, **fennel seed oil**, and **curcumin** have been shown to target these causes.

In clinical trials, they significantly reduce bloating, gas, feelings of excessive fullness, stomach distension, abdominal pain and discomfort. •

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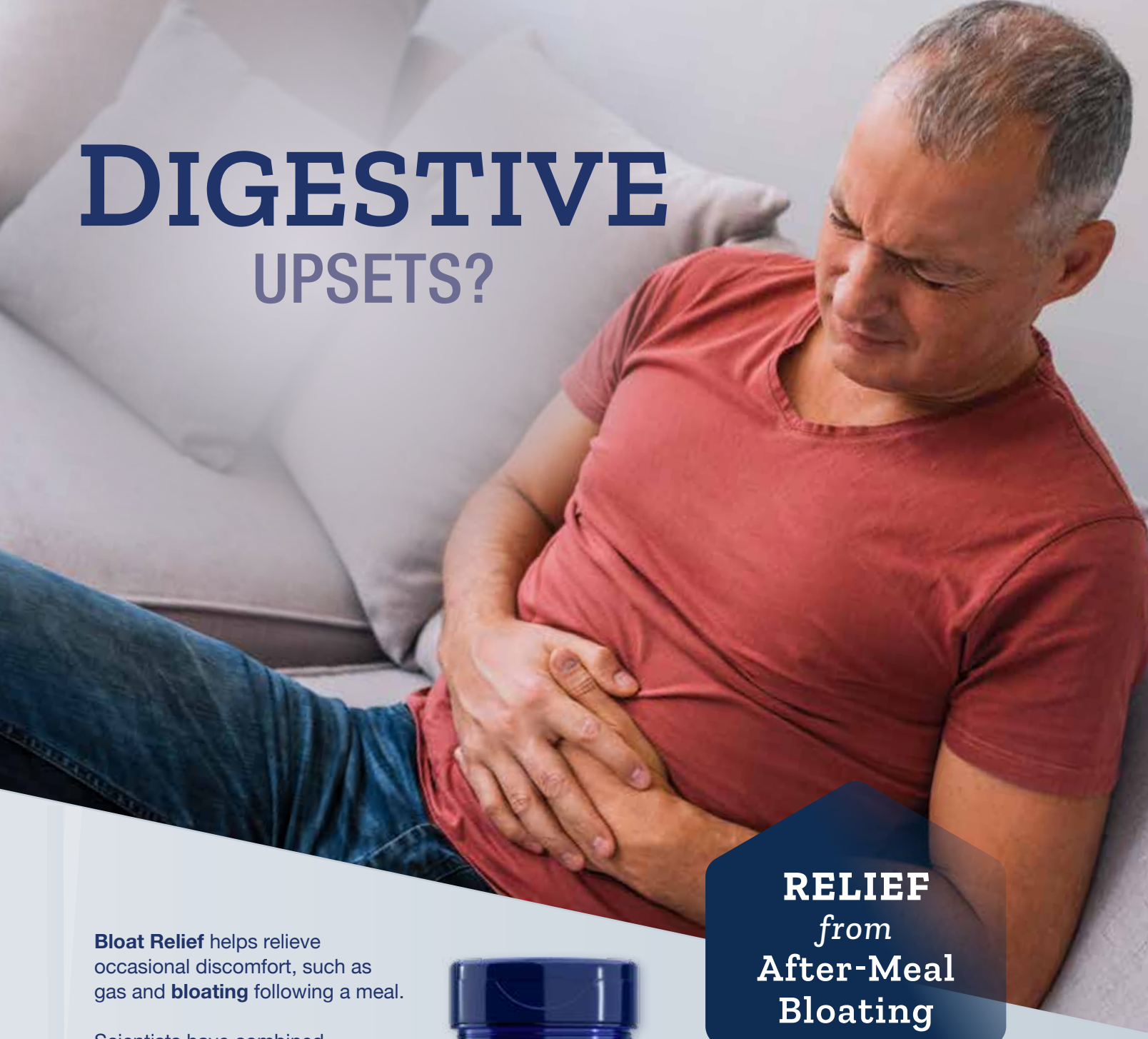
DIGESTIVE UPSETS?



RELIEF *from* After-Meal Bloating

Bloat Relief helps relieve occasional discomfort, such as gas and **bloating** following a meal.

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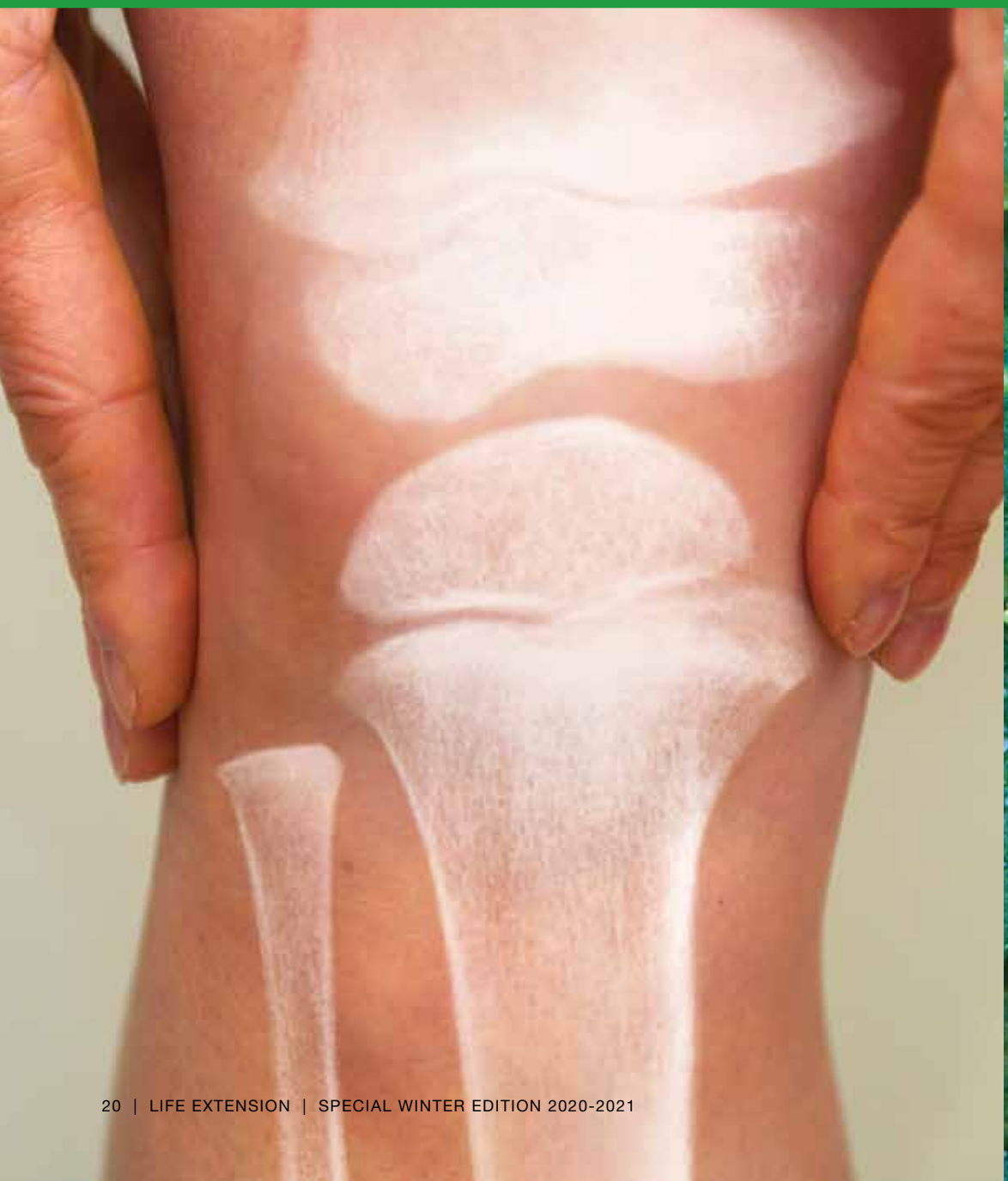
High-Dose VITAMIN K2 Builds New Bone

BY STEPHEN ROSS



With age, our bones get thinner and weaker.

This leads to increased **fractures** that are leading causes of disability as people age past **50 years**.[1]

The numbers are chilling. Within a year of suffering a hip fracture, up to **20%** of patients will die.[1] And almost *any* kind of broken bone increases the risk of death in older people.[2]

Physicians in **Japan** discovered a way to help prevent **bone loss** and protect against **fractures**.

For more than two decades they have been prescribing a ***high-dose* vitamin K2** in the form of **menaquinone-4** or **MK4**.[3]

This high-dose vitamin K, used as a **prescription drug** in Japan, is now available as a **dietary supplement**.

Vitamin K is found in small amounts in many foods and over-the-counter formulas. But at the ***high dose*** of **45 mg**, it has a profound impact, helping to:[4-11]

- Slow bone loss,
- Build *new* bone, and
- Reduce fracture risk.

In a two-year study on older people with **osteoporosis**, high-dose vitamin K2 cut the number suffering a vertebral **fracture** by **half**.[11]

Along with other nutrients known to support bone strength, **vitamin K2** plays an essential role in maintaining and helping to restore **bone density**.

What Causes Bone Loss?

To maintain **structure**, old bone is constantly being broken down, and new bone is being built up.

For the first decades of life, **bone density** (how tightly bones are packed with minerals) increases. Peak bone density and bone strength then plateau for about two decades.

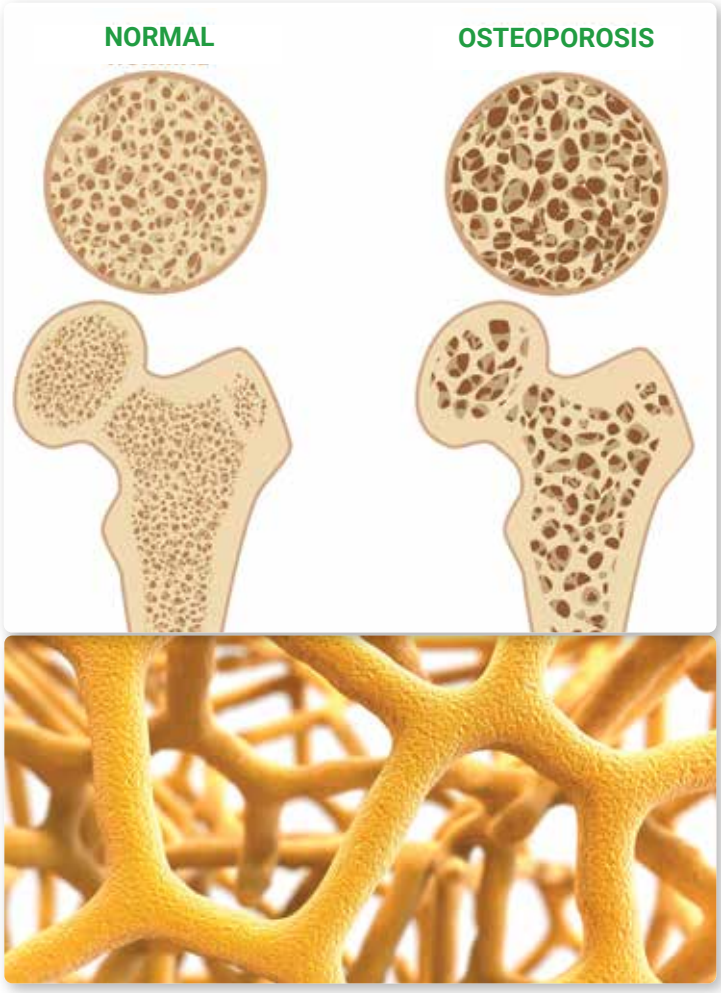
By age 40, bone density starts to fall and continues to decline into old age. In women, the speed of bone loss accelerates with the onset of **menopause**.

That *drop* in bone-mineral density leads to a *reduction* in bone strength. Bones become brittle and prone to **fractures**, even from minor injuries (or **stress fractures** that occur during normal use).

The early stage of bones weakening is called **osteopenia**.

As **bone density** continues to drop, **osteoporosis** develops, which means "***bone full of pores or holes***."

Most people don't know they have **osteopenia** or **osteoporosis** until it's too late—when they suffer a **fracture**.



High Doses of Vitamin K2

The encouraging news is there *is* something we can do about age-related bone loss and risk of fractures.

Vitamin K2 has been used to treat **osteoporosis** in Japan for decades.[3]

Research has confirmed that this specific form of vitamin K is critical for bone health and other aspects of healthy aging.

In low doses (60 mcg), vitamin K promotes normal blood clotting. This small amount of vitamin K is normally obtained from dietary sources.

Beginning in **1999**, scientists at **Life Extension**® recognized that *higher* doses of vitamin K can better keep **calcium in bones** and help prevent **calcification** of soft tissues such as heart valves, arteries, and brain cells.

As data accumulated over the past **21 years**, the suggested daily dose of vitamin K steadily increased to over **2,000 mcg**, which is far *higher* than the tiny amount needed for normal blood coagulation.

Vitamin K2 Safety Profile

What's interesting is how vitamin K functions to enable normal coagulation.

Once low doses activate **coagulation proteins** in the liver, then no matter how much more vitamin K is ingested, there is no excess coagulation/clotting risk. That's because when coagulation proteins are fully saturated with vitamin K, they cannot take up more vitamin K to cause greater coagulation potential.

With this understanding, the opportunity to use far ***higher*** vitamin K doses to build strong bones became an enticing reality.

So much so that Japanese doctors began prescribing **45,000 mcg** of **vitamin K2** and have verified profound improvements in bone health in older adults.[3]

Building New Bone

Bone density is influenced by two types of bone cells: **osteoclasts** and **osteoblasts**.

Osteo*clasts* break down old bone. Osteo*blasts* build new bone.

Healthy bone relies on a balance of activity between these two types of cells. They constantly remodel **bone structure** while keeping **bone density** stable.

As we age, this balance is lost. Osteo*clast* activity outweighs osteo*blast* activity. As a result, bone is broken down faster than new bone can be built up. As bone density drops, **osteopenia** and **osteoporosis** manifest.

Vitamin K2 appears to restore healthy balance. In preclinical studies, it promotes an increase in bone-building **osteoblast** activity and *reduces* **osteoclast** activity.[12,13] With this balance restored, more bone is built, less is destroyed, and **bone mineral density** is maintained or even *increased*.

In addition, in order to lay down new bone, osteoblasts need a protein called **osteocalcin**. This protein binds to **calcium**, helping osteoblasts turn calcium into healthy new bone.[13] Vitamin K2 helps convert osteocalcin into its *active* form.[13,14]

WHAT YOU NEED TO KNOW

Prevent Fractures with Vitamin K2

- Bone loss begins to occur in our 40s and progresses with advancing age.
- This weakening of bone can lead to osteoporosis and greatly increased risk of fractures, which can cause disability and dramatically increase risk of death.
- High-dose vitamin K2 has been used as a treatment for osteoporosis in Japan for decades.
- Vitamin K2 acts by several mechanisms to improve bone health in preclinical studies, including restoring balance to the process of bone breakdown and formation.
- Human trials have shown that daily intake of 45 mg (45,000 micrograms) of vitamin K2 maintains or increases bone density and reduces the risk of fractures.
- Other nutrients, including calcium and vitamin D3, also support bone health and help maximize vitamin K2's benefits.

Keeping Bones Strong

Human trials have tested the benefits of vitamin K2 on bone health.[4-11]

The results show that **high-dose** vitamin K2:

- Increases **active osteocalcin** levels required for new bone formation, and
- Maintains or increases **bone mineral density**.

Many of these studies have been performed in older people with **osteoporosis**. Even those already at this advanced level of bone loss benefit from oral **vitamin K2**.

One example comes from researchers in Japan.[11] They enrolled older individuals in a study who all had a diagnosis of **osteoporosis**. Patients were randomized to receive either **calcium** alone or calcium plus **45 mg** of **vitamin K2** daily.

Over the course of the two-year study, subjects who received *only* **calcium** continued to lose **bone density**, dropping by about **3%**.

A **10%** drop in bone density more than ***doubles*** the risk for **fractures** of the vertebra (the bones making up the spine) and hip.[15] This means that those treated only with **calcium** in this study (who lost **3%** of bone density) increased their risk of **fracture**.

Vitamin K2 and Bisphosphonates

The **bisphosphonates** are a group of drugs prescribed to slow bone loss in osteoporosis. They include medications such as **alendronate**, **risedronate**, and others.

Research shows that vitamin K2 does *not* interfere with bisphosphonates and can safely be used at the same time. There are even some data to suggest that they may have an ***additive*** effect, protecting bone density better together than either one alone.[28]

On the other hand, people receiving **high-dose vitamin K2** in addition to **calcium** largely maintained their bone mineral density. They also benefited from a significant *increase* in levels of **active osteocalcin**.

Reducing Fracture Risk

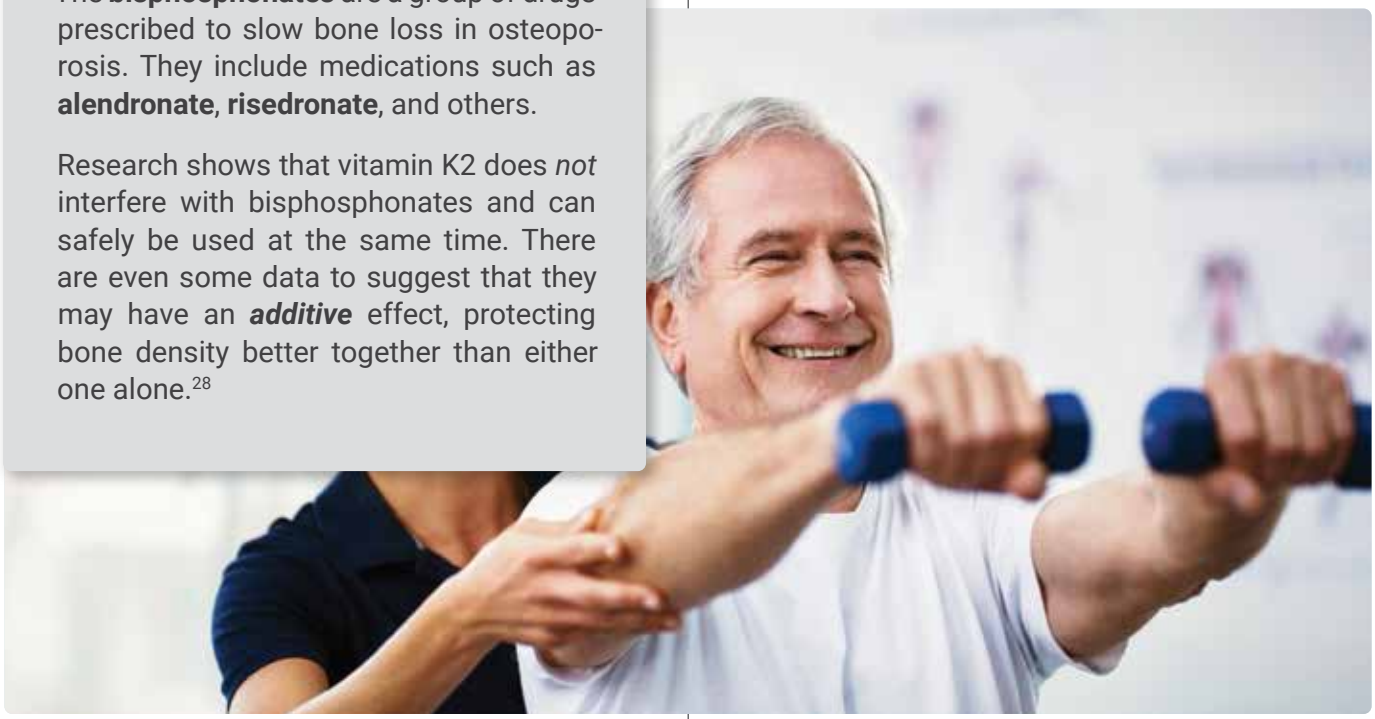
The scale of osteoporosis and related fractures is staggering.

Worldwide, as many as ***one-third*** of women and **one-fifth** of men over **age 50** will suffer an **osteoporotic fracture**.[1] And after suffering one fracture, the risk of future fractures increases by a whopping **86%**.[1]

Fractures of the **hip** and **vertebra** in particular are associated with pain, loss of mobility, and risk of death.[1] For example, people who suffer a **vertebral fracture** have an **8-fold** increase in mortality compared to other individuals their age.[1]

In the Japanese study on older people with osteoporosis, **30%** of those receiving only calcium suffered vertebral fractures during the two years of the study. But only **14%** of those also receiving high-dose **vitamin K2 + calcium** had a vertebral fracture.[11] (These study subjects did not receive supplements like **vitamin D** and **magnesium**, also needed to protect aging bones.)

Another Japanese clinical trial found that **45 mg** of vitamin K2 daily maintained bone mineral density and reduced the risk of fractures.[6]



Nutrients That Work *with* Vitamin K2

As in all aspects of health, no one nutrient is enough on its own. Vitamin K works with other **nutrients** to form healthy bone.

The following nutrients have been shown to keep **bone-density** levels up and to maximize the benefits of vitamin K2:

- **Calcium** is the major mineral that forms the hard, strong matrix of bone. Adequate calcium is needed so that osteoblasts have it readily available to build bone tissue.
- **Vitamin D** helps absorb calcium from the gut after a meal and stimulate the production of the protein osteocalcin, needed to form new bone.[14]
- **Magnesium**, like calcium, makes up the mineral matrix of bone. Adequate levels are needed to maintain healthy bone density.[16]
- **Zinc**, **Manganese**, **Silicon**, and **Boron**. These minerals have been shown to be important for optimal bone formation and health. *Low* intake of each of these minerals is associated with bone *loss*, and increased intake improves bone health in animal models and in humans.[17-27]

Taken together with high doses of vitamin K2, these nutrients protect against bone loss and fractures.

Summary

As our bones become thinner and weaker with age, the risk of dangerous and life-threatening **fractures** increases.

High-dose vitamin K2 has been used to treat the bone disease **osteoporosis** for decades in Japan.

Clinical trials demonstrate that daily intake of **45 mg** of vitamin K2 maintains or increases bone-mineral density and reduces the **risk of fractures**.

Along with other vitamins and minerals crucial for bone health, vitamin K2 is a powerful tool to help build stronger, healthier bones well into old age. •

Cardiovascular Disease Benefits

Vitamin K2 promotes new bone growth in part by increasing **calcification**, the buildup of calcium deposits, in the bone.

However, in soft tissues, calcification can be extremely dangerous. In blood vessels, it leads to the buildup of atherosclerotic plaques associated with **cardiovascular disease**.

Remarkably, research has shown that while vitamin K2 causes beneficial calcification in bones, it *prevents* harmful calcification in soft tissues, including blood vessels.[29,30] This occurs because it activates matrix Gla protein, which *inhibits* **calcification** of blood vessels.

For this reason, vitamin K2 may be protective against cardiovascular disease.[31]

In addition, while **vitamin K1** is used to help blood clot in response to blood vessel injury, vitamin K2 has not shown any impact on clotting or **coagulation**.[32] Still, anyone taking warfarin, a powerful anticoagulant, should consult a physician before deciding to take any form of vitamin K.

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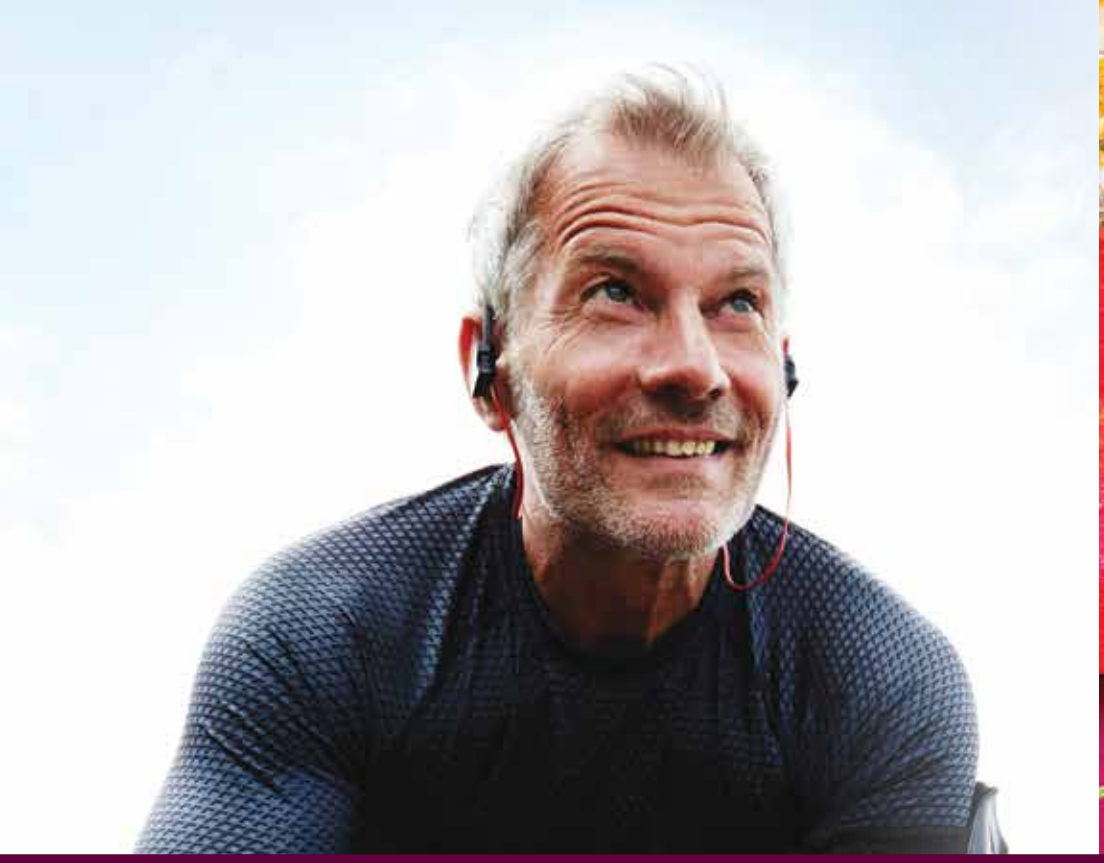


FISETIN: A Longevity Senolytic

BY ZACH WHITE

For decades, scientists have searched for compounds that can slow degenerative aging processes.

A recent focus is a plant extract called **fisetin**.

Found in strawberries, apples, and other plants, **fisetin** has a range of benefits that may increase **longevity**.[1,2]

Fisetin has been shown to:

- Function as a **senolytic**, clearing away dysfunctional senescent cells and allowing healthy cells to thrive,[3]
- Protect the **brain** in various models of neurodegenerative disorders, [2,4-9]
- Improve outcomes in people who have suffered **strokes**,[10]
- Help prevent **malignant** changes in cells,[11-14] and
- Help fight **obesity** and **type II diabetes**.[15-17]

Several human trials are currently underway.

The challenge up until now was that **fisetin** is converted to an *inactive* form in the digestive tract. This means very little is ***absorbed*** into the blood stream.

For the first time, scientists have developed a low-cost method to increase **absorption** up to **25 times** *higher*,[18] thus enabling **fisetin** to be distributed throughout the body.

What Is Fisetin?

Fisetin, a flavonoid, is found in various fruits and vegetables including strawberries, apples, persimmons, grapes, and onions.

Its benefits overlap with some other flavonoids, including green tea catechins and quercetin. But it has its own unique set of biological properties.

Most notably, a recent study found **fisetin** to be the ***most potent senolytic*** compound among a group of flavonoids that were tested.[3] Senolytics are at the center of today's anti-aging research.

Fisetin Extends Lifespan

When cells become old or dysfunctional, they're supposed to die off to make room for new cells. But as we age, many cells become **senescent** instead.

What this means is that these cells lose their ability to divide or perform basic functions and refuse to die. Some scientists refer to senescent cells as "zombie cells."

Senescent cells don't just linger around. They pump out toxic compounds that degrade nearby cells and incite **chronic inflammation** that causes systemic damage.[19]

Cellular senescence has become a major target for anti-aging research. Preclinical studies indicate that compounds called **senolytic**s remove senescent cells and can slow or even reverse aging processes.[3,20-22]

Recent research has found that fisetin is an exceptionally powerful **senolytic**. When compared to other plant compounds, including quercetin, **fisetin** was **the most effective** at removing senescent cells, both in cell culture and in mice.[3]

The effects are dramatic. Mice given fisetin lived an average of about 2.5 months longer, an almost **10% extension of lifespan**—even when treatment was started at the **human** equivalent of **75 years** of age.[3]

The **Mayo Clinic** has begun clinical trials to study the ability of fisetin to reduce senescent cell burden in aging humans.[23]

Anti-Aging Properties

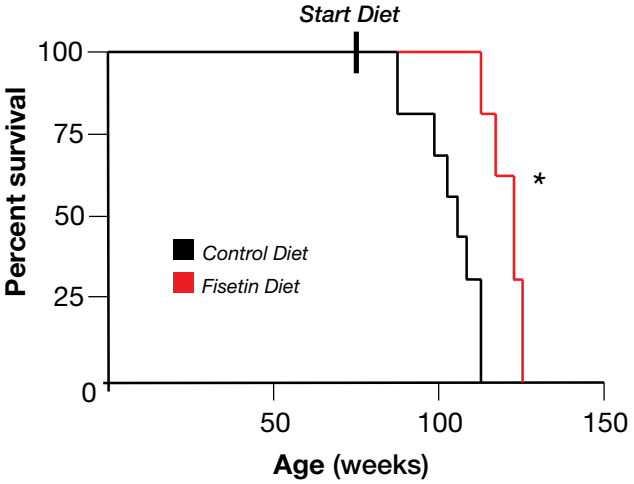
Sirtuin proteins are another anti-aging target.[24,25] These cellular protectors are found in all cells in the body, and are vital for keeping cells performing at peak level.

Sirtuin function tends to ***diminish*** with age. But fisetin activates **sirtuin** function in cells, countering this decline.[26-30] In various animal models, sirtuin activation has been shown to ***extend lifespan*** significantly.[24,25,31,32]

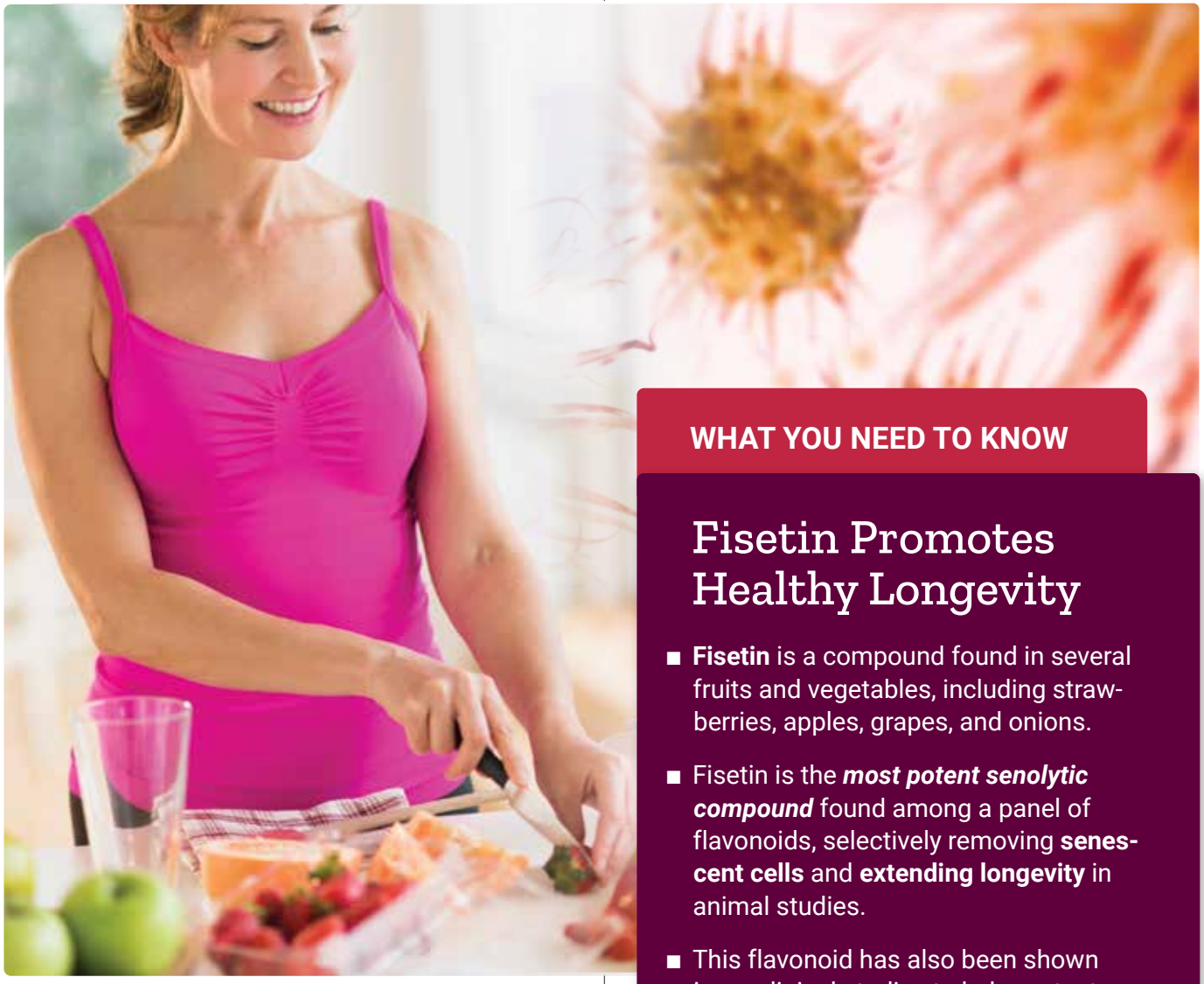
Fisetin may protect against aging in other ways:

- It reduces **inflammation**, a driver of many chronic illnesses and even of aging itself.[2]
- It mimics some of the effects of a **calorie-restricted diet**, which has been shown to boost resistance to disease and increase lifespan.[1,2,29,34]
- It helps prevent **oxidative damage** that leads to accelerated aging and degenerative disease.[33]

Longer lifespan in old mice with fisetin supplementation.



Mice given **fisetin** by itself lived an average of **10% longer** even when treatment was started at the human equivalent of 75 years of age.[3]



Preventing Obesity and Diabetes

Obesity leads to a skyrocketing risk of metabolic disorders such as **type II diabetes**. It also increases the risk for cardiovascular disease, cancer, dementia, and many other disorders.

Preclinical studies show that fisetin appears to act as a kind of "**metabolism control switch**," reducing **fat cell** accumulation and suppressing activation of the protein **mTOR**, which is linked to weight gain. In mice fed a high-fat diet, fisetin *prevented* increase in body weight and accumulation of harmful white fat tissue.[15]

Fisetin also helped fight fat accumulation in the livers of animals fed a high-fat diet, a common occurrence with metabolic disease that can compromise liver function and lead to **fatty liver disease**.[35-38]

WHAT YOU NEED TO KNOW

Fisetin Promotes Healthy Longevity

- **Fisetin** is a compound found in several fruits and vegetables, including strawberries, apples, grapes, and onions.
- Fisetin is the ***most potent senolytic compound*** found among a panel of flavonoids, selectively removing **senescent cells** and **extending longevity** in animal studies.
- This flavonoid has also been shown in preclinical studies to help protect against cancer, type II diabetes, and obesity, and in a human study to improve outcomes in stroke victims.
- Taken orally, pure fisetin is converted to an inactive form in the body. But scientists have discovered that combining it with **galactomannans** from fenugreek prevents that from happening.
- A new formulation boosts the bioavailability of fisetin by **25 times**, allowing more of it to circulate throughout the body, promoting health and supporting longevity.

Fisetin may provide benefits for those already suffering from **type II diabetes**.

In rodent models of diabetes, fisetin lowers body weight and leads to improved **glucose control** with lower hemoglobin **A1c** levels, a marker of blood sugar regulation over time.[16,17]

Poorly controlled **diabetes** often causes disabling or life-threatening complications throughout the body. In mice, fisetin significantly ***reduces the severity of diabetic complications***, including slowing the progression of cataracts, preventing kidney damage, and improving kidney function.[16,39]

A human trial of fisetin's ability to protect **kidney** function, particularly in diabetes patients, is currently underway.[40]

Brain Benefits

People who suffer from a **stroke** are often treated with medication to dissolve the clot blocking blood flow to the brain. This can save a patient's life, prevent damage to the brain, and even reverse the symptoms of stroke in some patients.

But ER doctors are working against the clock when treating acute (ischemic) stroke. The best chances of success occur when treatment begins within **three hours** of the onset of symptoms.[41] Many people suffering a stroke are treated too late and suffer permanent neurological injury (and paralysis).

A recent study shows that *combining* clot-dissolving medication with **fisetin** significantly extends the treatment window.[10]

Patients receiving fisetin in addition to usual treatment up to **five hours** after a stroke had neurological outcomes as good as those treated within **three hours**. This extension of the therapeutic window means that many stroke victims who would otherwise suffer permanent loss of brain function have a better chance of recovery.

Fisetin has also shown **neuroprotective** benefits in animal models of Alzheimer's disease, Parkinson's disease, ALS (amyotrophic lateral sclerosis), and other brain pathologies, reducing the severity of disease and improving cognitive function.[2,4-9]

Fighting Cancer

Fisetin has shown potential in preventing cancer and limiting the growth and spread of existing tumors in preclinical studies. Among its **anti-cancer** properties:

- Fisetin induces **apoptosis**, or programmed cell death, in cancer, which can facilitate removal of tumor cells.[47-50]
- As an **anti-inflammatory**, fisetin reduces compounds that contribute to chronic inflammation and cancer progression.[42-45] In a study of patients with colorectal cancer, fisetin reduced levels of pro-inflammatory mediators.[46]
- Fisetin enhances **autophagy**,[51] cellular housekeeping that keeps cells functioning normally. Enhanced autophagy can *inhibit* cancer cell survival.
- Fisetin helps prevent **angiogenesis**, the formation of new blood vessels, in cancer, starving tumor cells of oxygen and glucose.[52,53]
- Fisetin helps prevent **oxidative** damage which can contribute to DNA mutations and cancer development.[42,43]
- Fisetin may inhibit cancer cell migration and **metastasis**, the spread of cancer to a different part of the body.[54]

Improved Bioavailability

In its pure form taken orally, there's a problem with fisetin: Once it reaches the gut, *enzymes* in the body rapidly modify it into a form which is **inactive** and all but useless.

Scientists have discovered a way around this problem. By combining it with natural compounds called **galactomannans** isolated from the herb **fenugreek**, fisetin is protected from being modified in the intestinal tract. It remains active and can be readily ***absorbed*** into the bloodstream.

In a recently conducted study, researchers found that the newly formulated **fisetin-galactomannan** combination, using a patented green technology, increases bioavailability (how much is absorbed and circulates) in people by ***25 times***.[18]

This opens a brand-new door in enabling aging people to derive meaningful benefits by supplementing with a low-cost nutrient.

Summary

Fisetin is a compound found in many plants, including strawberries and apples.

It is the **most effective senolytic** compared to a panel of flavonoids, removing aged, dysfunctional **senescent cells** in preclinical studies. This may help improve function in older age, shield against chronic disease, and increase healthy longevity.

In mice, fisetin alone extended lifespan by approximately **10%**.

Extensive research also demonstrates the potential of fisetin to help protect against cancer, stroke, obesity, type II diabetes, and other metabolic disorders.

A new fisetin formula compounds it with **fenugreek**, which protects it from inactivation in the gut. This allows more fisetin to be ***absorbed*** and distributed throughout the body for systemic benefits. •

(Turn page to review options for using fisetin as a senolytic and to view references.)

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(Additional references on page 38.)

OPTIONS TO REMOVE SENESCENT CELLS

Most of you are reducing your senescent cell burden by:

- **Two-day-a-week fasting (not eating 2 days each week) or time-restricted eating (fasting 16-18 hours most days)** and/or some other form of dietary restriction,
- Several times a year dosing using **dasatinib + quercetin** and/or,
- Weekly dosing using **black tea theaflavins + quercetin + apigenin**.

Fisetin is arguably one of the most focused, targeted senolytic agents, based upon current science. For the first time, people can obtain it in **bioavailable form** as opposed to taking over 1,400 mg a day of fisetin by itself and hoping enough is **absorbed** into your bloodstream.

For those who want to continue with a **weekly** senolytic program, taking seven capsules once-a-week of **bioavailable fisetin** along with a **black tea theaflavins + quercetin + apigenin** formula is an option.

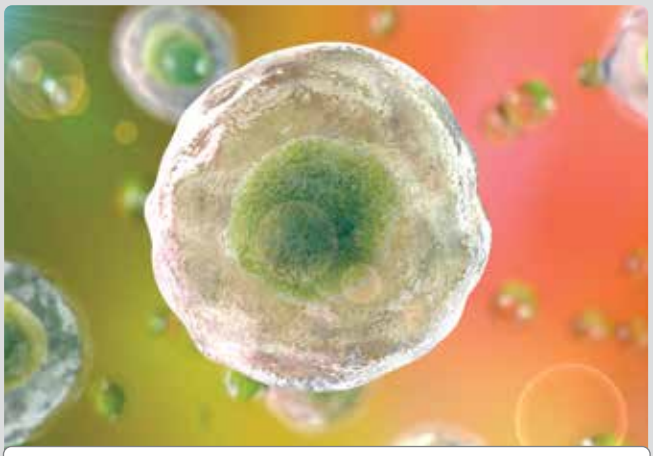
Alternatively, you may also take the bioavailable **fisetin** dose **daily** for its other benefits and continue with weekly **black tea theaflavins + quercetin + apigenin**.

There is potential benefit to daily senolytic as this is how it happens in younger people with strong immune systems that constantly remove senescent cells.[55]

Studies are planned for using bioavailable fisetin on differing dosing schedules to ascertain the ideal protocol to removing senescent cells and reducing the "senescent associated secretory phenotype" (SASPs).

While the longevity data on **dasatinib** is compelling, some people experience mild flu symptoms or GI upsets, whereas **fisetin** does not cause these unpleasant side effects.

We look forward to results from human trials to identify the optimal senolytic protocol for aging persons to follow. This may involve several senolytic compounds based on individual response rates as measured by the "senescent associated secretory phenotype," skin punch measures of senescent fibroblast cells, or other senolytic measuring methods being explored.



Highlights from Recent Study

- **Senescent cell production rate increases with age** due to accumulation of mutations, telomere damage, other factors triggering cell senescence.
- **Senescent cells catalyze their own production** by paracrine and bystander effects.
- **Senescent cell** removal decreases with age due to decline in immune surveillance functions.
- **Senescent cells reduce their own removal rate**.

Karin O, Agrawal A, Porat Z, et al. Senescent cell turnover slows with age providing an explanation for the Gompertz law. Nat Commun. 2019 Dec 2;10(1):5495.

Senescent Cell Removal Declines with Aging

Senescent cells turn over in **five** days in 3-month-old mice but take **25** days in 22-month-old mice. This model predicts a vicious cycle where senescent cells accumulate faster and are degraded slower.

At the point of **30% senescent cell load** animals often appear to reach tipping point **resulting in death**.

"Our results suggest that treatments that remove senescent cells can therefore have a double benefit: an immediate benefit from a reduced senescent cell load, and a longer term benefit from increased senescent cells removal."

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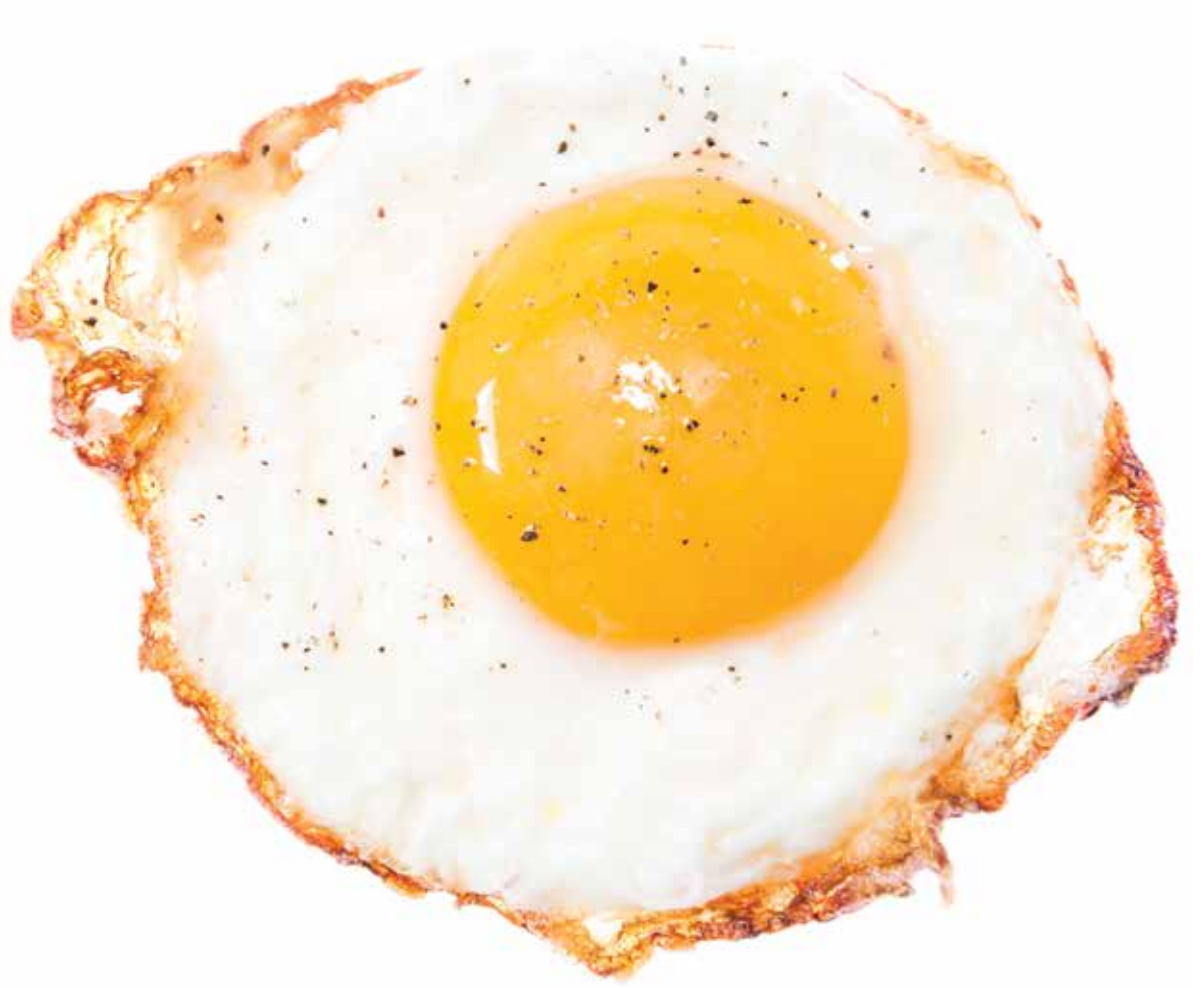

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FISETIN

The Longevity Flavonoid

Fisetin, a flavonoid found in strawberries and apples, is currently being studied for its effectiveness as a **senolytic** in humans.[1]

In preclinical studies, fisetin:

- Mimics effects of **calorie reduction**[2]
- Targets longevity pathways[2-6]
- Extends lifespan of mice by about **10%**[7]
- Removes **senescent** cells through **senolytic** action[7]
- Suppresses excess **mTOR** activation[8]

Fisetin is poorly *absorbed* due to its breakdown in the small intestines.

Bio-Fisetin supports against this breakdown by enclosing **fisetin** with a compound from the fenugreek herb.

A **human** trial showed **bioavailability** of this new **fisetin** compound increased up to ***25 times*** compared to fisetin by itself.[9]

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

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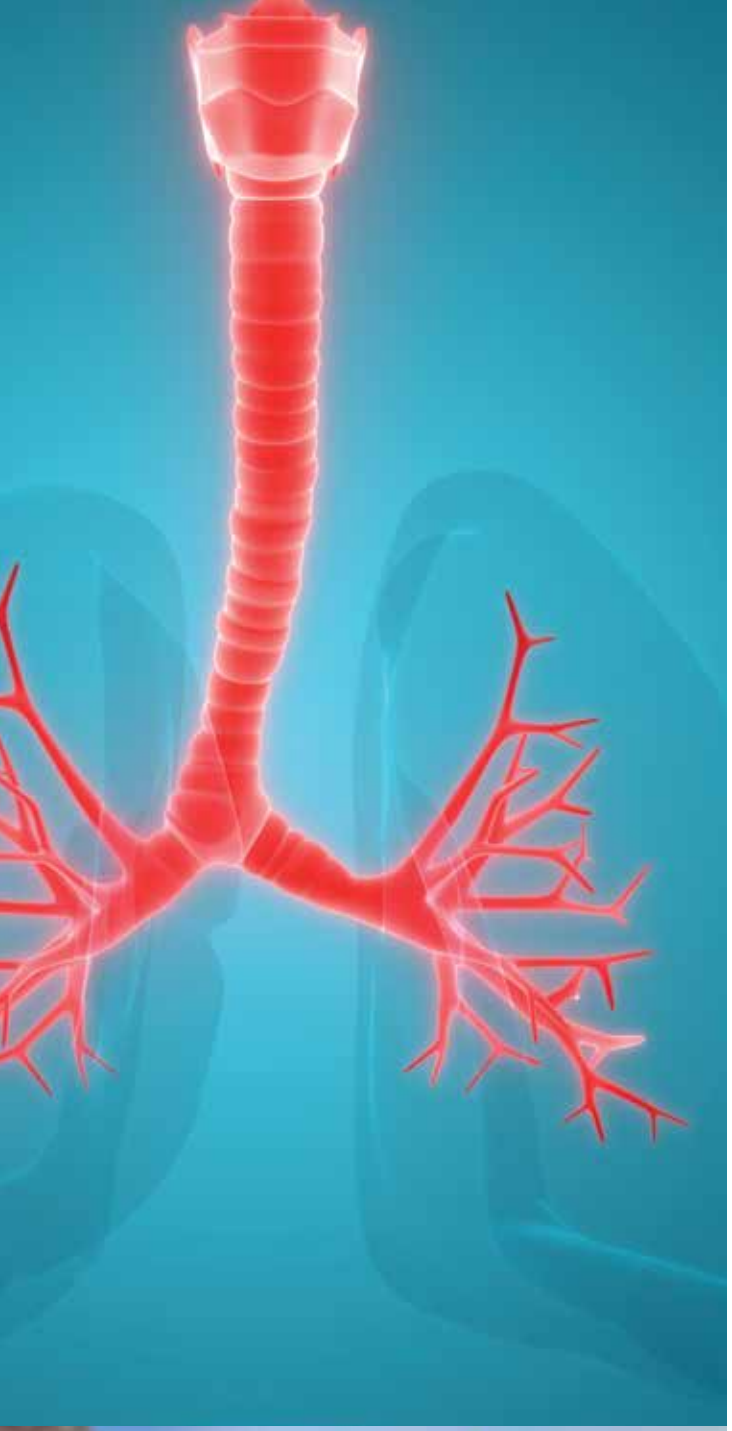
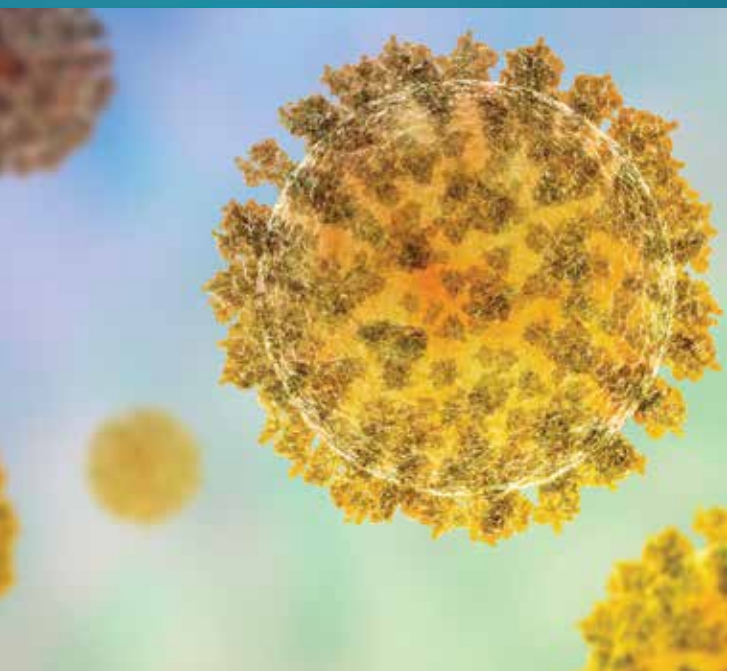




N-acetyl-L-cysteine is an amino acid derivative that breaks down excess mucus in air passages.

Used by physicians for decades, **N-acetyl-L-cysteine** has a wide variety of benefits, especially helping to protect the lungs and airways of the **respiratory tract**.

Known by many as **NAC**, N-acetyl-L-cysteine has been shown to reduce the number of harmful **pathogens**, including bacteria *and* viruses.[1-6]

Clinical studies have shown that **NAC** can help treat or prevent worsening of **chronic bronchitis** and **acute respiratory distress syndrome**, an often fatal complication in patients with pneumonia or other severe lung infections.[7-12]

In patients with **chronic obstructive pulmonary disease (COPD)**, N-acetyl-L-cysteine has been associated with lower rates of exacerbations (periods of worsening of symptoms) and fewer days spent in the hospital.[4,13-18]

Most individuals gain benefits from using **600 mg** to **1,800 mg/day** in divided dosages.

What Is N-Acetyl-L-Cysteine?

N-acetyl-L-cysteine (NAC) is a precursor of **L-cysteine**, the amino acid cells need to produce one of the most powerful antioxidants in the body, **glutathione**.[19,20]

Found in every cell in the body, glutathione fights the **oxidative stress** that is closely associated with many age-related chronic diseases.[21]

But scientists have found that N-acetyl-L-cysteine does much more than this. It also protects the **respiratory system** from a number of different pathogens and diseases.

Controlling Excess Mucus

Healthy lungs have a built-in cleaning and protection system.

A small amount of **mucus** is secreted to coat the walls of the airways. This mucus traps inhaled particles, many of which can be irritants, infectious, or worse. Then, tiny projections called **cilia** on the surface of cells lining the airways sweep away the mucus and trapped particles, keeping airways clear and protecting the lungs from potential pathogens.

Many conditions, from allergies to infection to lung disease, can cause this system to become dysfunctional, leading to the secretion of large amounts of mucus.[22]

When **excess mucus** accumulates, it becomes sticky and hard to remove, leading to difficulty breathing. This complicates many lung conditions, including bronchitis, emphysema, asthma, cystic fibrosis, and lung infections.[22]

Doctors have been using inhaled **N-acetyl-L-cysteine** to reduce mucus since the 1960s.[23] It breaks down mucus secretions, making them less dense and sticky.

N-acetyl-L-cysteine also reduces the *thickness* of the mucus.[3] It does this by reacting with bonds within the mucus proteins and thinning the mucus.[4,24]

This helps clear the airways *and* makes it easier for the cilia to sweep away mucus and trapped particles.[3]

Reducing Oxidative Stress

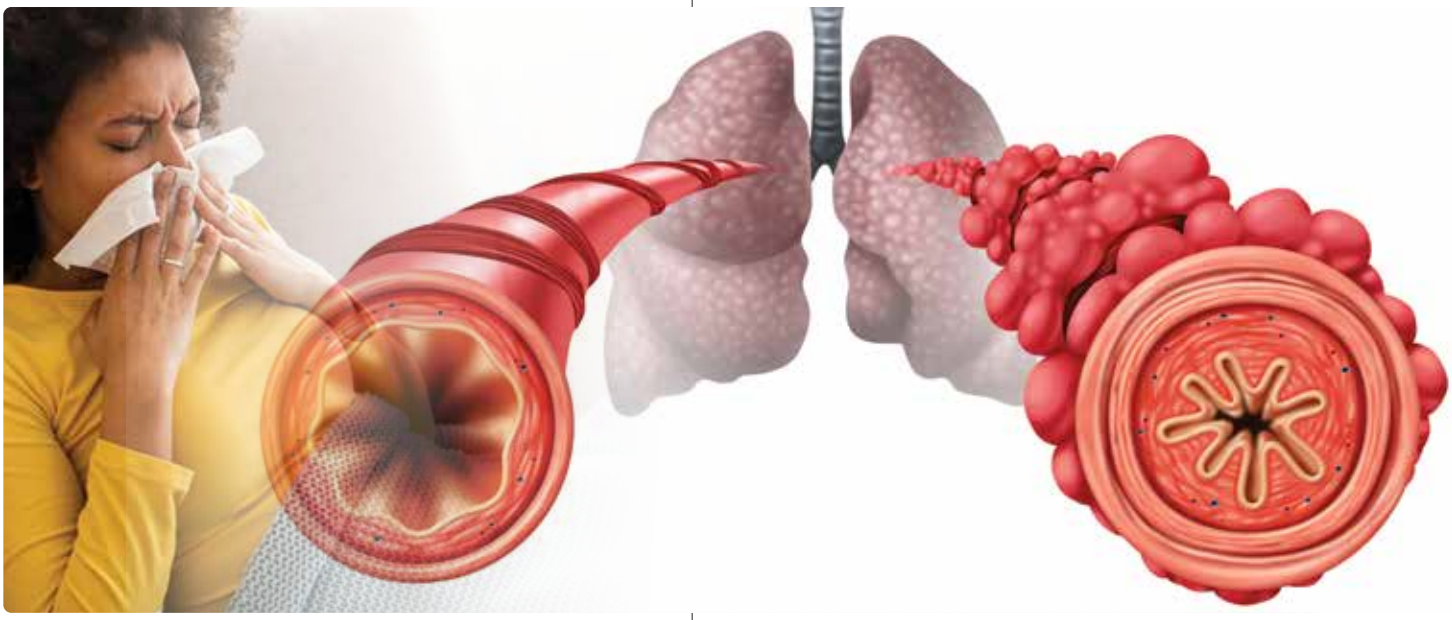
N-acetyl-L-cysteine is a highly effective precursor to the antioxidant **glutathione**, which reduces oxidative stress and free-radical tissue damage.[3,4,24]

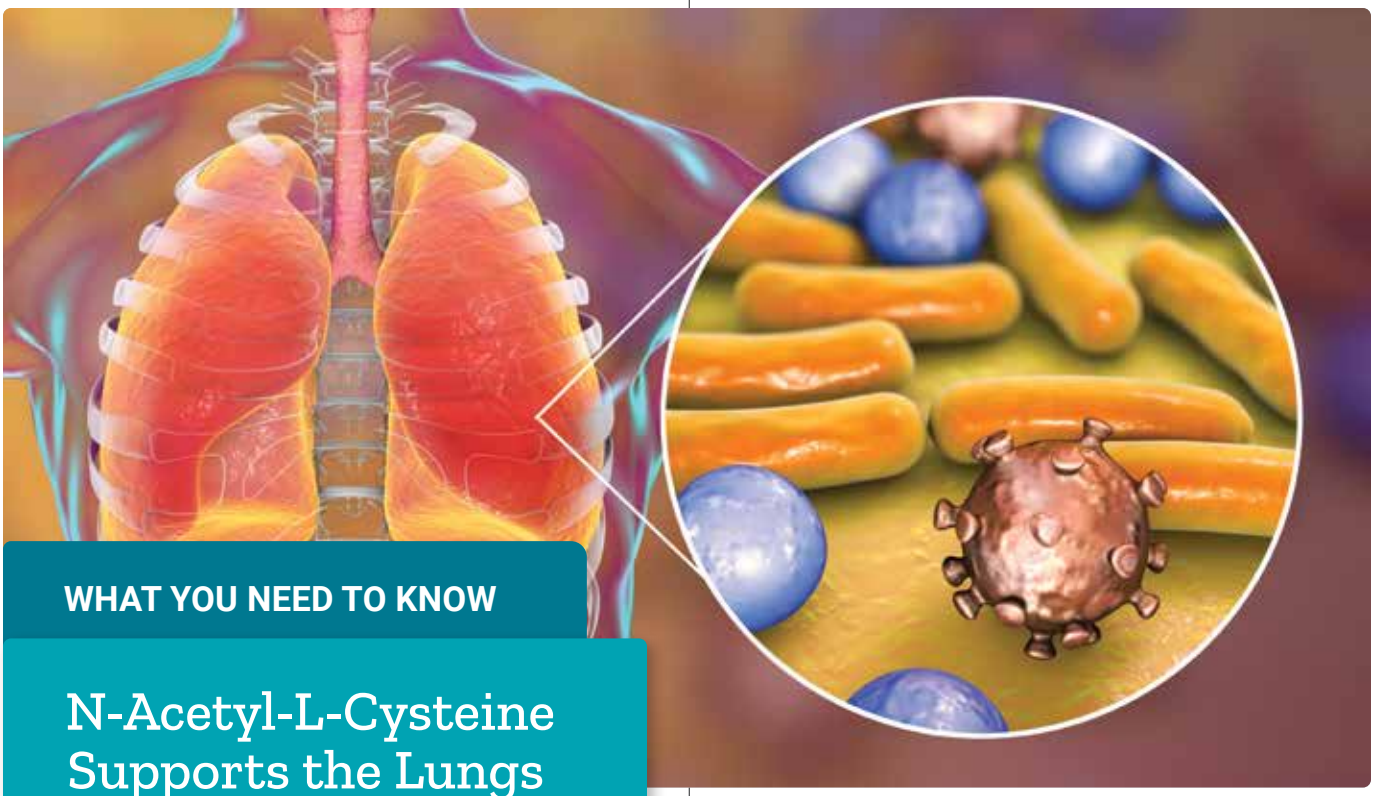
Taken orally, NAC is rapidly absorbed and distributed throughout the body, where it provides the building blocks for cells to produce their own glutathione.

N-acetyl-L-cysteine is also a **direct antioxidant** itself. Even before conversion into glutathione, it scavenges free radicals that could otherwise cause damage.[4]

Oxidative stress is a common contributor to many disorders of the respiratory system, from **infection** to **chronic obstructive pulmonary disease** (COPD), disorders of the lungs that cause difficulty breathing.[4]

By bolstering antioxidant reserves, and thus reducing oxidative stress, N-acetyl-L-cysteine offers powerful protection to the lungs.





WHAT YOU NEED TO KNOW

N-Acetyl-L-Cysteine Supports the Lungs and Airways

- **N-acetyl-L-cysteine** is a precursor to **glutathione**.
- It reduces and thins excess **mucus** production in the airways, which can be a major contributor to lung problems in infection and other conditions.
- N-acetyl-L-cysteine also reduces harmful inflammation and could help prevent colonization by **viruses** and **bacteria** in the lungs.
- Through all these mechanisms, N-acetyl-L-cysteine supports healthy **respiratory tract** function and may prevent or treat bronchitis, chronic obstructive pulmonary disease, acute respiratory distress syndrome, and respiratory tract infections.
- Typical daily doses of N-acetyl-L-cysteine range from **600 mg** to **1,800 mg** in divided doses.

For example, in COPD such as **emphysema**, oxidative stress in the lungs contributes to inflammation, abnormal constriction of the airways, fluid in the lungs, excess mucus secretion, and other tissue damage.[4] N-acetyl-L-cysteine reduces oxidative stress and the damage it does while also reducing mucus volume and thickness.

Stopping Infectious Pathogens

N-acetyl-L-cysteine has been shown to reduce the number of harmful **pathogens**, including bacteria and viruses.

In the case of harmful **bacteria**, N-acetyl-L-cysteine makes it hard for them to gain a foothold and cause infection.

In vitro experiments show that N-acetyl-L-cysteine prevents bacteria from adhering to cells lining the airways.[5,6]

One of the ways it accomplishes this is by disrupting **biofilms**, slimy coverings that many disease-causing bacteria form around themselves. These films prevent immune cells from recognizing and gaining access to the bacteria. They also make it difficult for antibiotics, antibodies, and other helpful compounds to get to the bacteria.

N-acetyl-L-cysteine blocks the formation of biofilms and destroys existing ones, impeding the ability of bacteria to survive in the airways.[2,3]

The protection from pathogens also extends to **viruses**.

One cell study evaluated **respiratory syncytial virus**. Normally, this virus invades the cells lining the airways, growing rapidly and causing damage to the structure of the airways.

But treatment with N-acetyl-L-cysteine ***blocks the reproduction of the virus*** while restoring the normal structure and function of the cells lining the airways.[1]

Reducing Harmful Inflammation

By preventing free-radical damage, reducing pathogen colonization, and other mechanisms, N-acetyl-L-cysteine decreases harmful **inflammation**, which contributes to the symptoms of most respiratory disorders.

Preclinical studies show that N-acetyl-L-cysteine reduces the production of pro-inflammatory compounds and decreases the production of compounds that initiate **fibrosis** in the lung tissue, scarring that makes it difficult for the lungs to work properly.[25-27]

Respiratory Tract Disorders

N-acetyl-L-cysteine has shown success in treating a number of different respiratory conditions.

Chronic bronchitis is longstanding inflammation in the airways of the lungs caused by irritation and tissue damage. It's common in smokers but can also be caused by secondhand smoke, air pollution, and other inhaled irritants.

Several human studies have shown that oral intake of N-acetyl-L-cysteine reduces **exacerbations** (worsening or flare-ups) of chronic bronchitis *and* significantly improves symptoms.[11,12]

Chronic obstructive pulmonary disease (COPD) refers to disorders of the lungs that restrict airflow in the lungs, making it hard to breathe. It includes chronic bronchitis, emphysema, and severe asthma.[28,29]

Oxidative stress, inflammation, and excessive secretion of airway-clogging mucus play major roles in these conditions. Knowing that N-acetyl-L-cysteine helps prevent or treat *all three* of these problems, scientists have tested it to treat COPD.

In COPD patients, N-acetyl-L-cysteine use has been associated with clinical improvements. These include lower rates and decreased severity of exacerbations, and fewer days spent in the hospital for COPD exacerbations.[4,13-18]

Acute respiratory distress syndrome (ARDS) is a form of severe lung inflammation that causes fluid to leak into the lungs, preventing oxygen from getting into the body.

It occurs in critical illness, particularly in patients suffering from **pneumonia** or other serious lung infections. It often requires mechanical ventilation and typically results in a high mortality rate.

Animal studies show that N-acetyl-L-cysteine protects the lungs from injury and leads to significant improvements.[30,31] In clinical studies, patients with acute respiratory distress syndrome who were given N-acetyl-L-cysteine had shorter intensive-care-unit stays, and clinical improvements.[7-10]

Summary

N-acetyl-L-cysteine (NAC) is a precursor to the antioxidant **glutathione**. It helps prevent harmful oxidative damage and reduces inflammation.

In the lungs and airways of the **respiratory tract**, it reduces and thins excess **mucus** secretion and could help prevent colonization by harmful **bacteria** and **viruses**.

Through these mechanisms and more, N-acetyl-L-cysteine supports healthy respiratory function and provides protection against lung diseases, including **acute respiratory distress syndrome**, infections, and **chronic obstructive pulmonary diseases** like bronchitis and emphysema.

Most individuals gain benefits from using **600 mg** to **1,800 mg/day** of N-acetyl-L-cysteine in divided dosages. •

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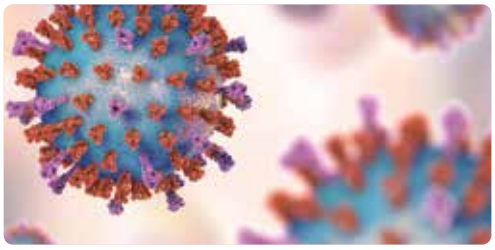

THWART POST-MEAL BLOATING

Up to **30%** of people complain about after-meal **bloating**. Researchers have identified **plant compounds** that relieve gastrointestinal distresses.

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PROTECT RESPIRATORY FUNCTION

NAC (N-acetyl-L-cysteine) helps prevent **viruses** and **bacteria** from adhering to the lining of the lungs, while reducing excess airway mucus.