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July 2022

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References

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A Case for Higher-Dose Melatonin



WILLIAM FALOON

On February 1, 2022, the *Journal of the American Medical Association (JAMA)* published a report showing that **melatonin** consumption “**significantly increased**” from **1999** to **2018** in the United States.¹

The authors point to this trend of “**self-administered**” melatonin as a reason to raise “**safety concerns**” about the lack of long-term clinical data. They make insinuations about the **poor quality** of melatonin supplements sold by certain commercial companies.

Concerns were also raised about insufficient study of people taking **melatonin** in nightly doses above **5 mg**.

It was **30 years** ago when our **Life Extension** group introduced the world to **melatonin**. We provided purified melatonin to researchers for **human** studies, and to our supporters.

We’ve had interactions with thousands of people who have used a wide range of melatonin potencies since we launched it in **1992**.

Rather than defend our long-term observed safe use of melatonin, this article will provide a rationale for some people to consider **higher** doses. I’ve self-experimented with these higher potencies for the last **two years** without experiencing adverse reactions.

The main reason I increased my nightly melatonin dose is the potential for **immune** benefits.²

In reviewing evidence about **higher-dose** melatonin, I recalled our **40-year** history of erring on the side of **safety** when introducing health-promoting compounds.

Below are examples of **dosage increases** of nutrients that **Life Extension** helped pioneer over the decades:

<u>Ingredient</u>	<u>Initial Dose</u>	<u>Current Average Dose</u>
CoQ10	10-30 mg	100-200 mg
Vitamin D	400-800 IU	2,000-5,000 IU
Resveratrol	20 mg	100-250 mg
Vitamin K	45-65 mcg	2,000-45,000 mcg
NAD⁺ precursor (nicotinamide riboside)	100 mg	300 mg

These **higher** potencies are made practical by price reductions for ingredients like **CoQ10** and **resveratrol**.

CoQ10 costs a fraction of what it did when **Life Extension** introduced it in **1983**, as does **resveratrol** that we launched in **2003**.

Given our history of using published data to increase suggested doses, I decided to try **50 mg** of **melatonin** each night and found some **sleep improvement**.

I’ve since lowered my overall melatonin **dose** to incorporate more **sustained-release** formulas, so my average nightly dose is now around **20 mg**.

This article describes what researchers are finding as it relates to additional benefits that may be achieved using a wide range of **melatonin** doses.

The phrase “*sleep like a baby*” refers to tranquil, deep sleep patterns like those young children typically enjoy.

What few people know is that nighttime **blood levels** of **melatonin** in **children** ages **1 to 3 years** are very **high** and then progressively **drop by 80%** during the remainder of childhood.³

Total melatonin secretion further declines with increasing **age**, beginning perhaps as early as the third decade of life.^{4,5}

Data like these prompted some physician-scientists to hypothesize that adults might benefit from **higher** potencies of melatonin when dealing with serious illnesses.

While many studies support some **sleep-enhancing** properties of **low-** and **moderate-dose** melatonin,^{6,7} lacking are tightly controlled human studies measuring the nocturnal effects of **high-dose** melatonin.

What are not missing are an abundant number of studies describing the potential of **melatonin** to help prevent and combat **cancer**.

Melatonin and Cancer

In the early 1990s, I went on national TV talk shows to announce the **lifesaving** benefits of **melatonin**. The data back then showed that melatonin improved **immunity** and might prevent and/or help fight certain **cancers**.^{8,9}

Move forward to **2022**, and there are over 3,000 published studies investigating the potential of **melatonin** to be **useful** in **cancer prevention** or as an **adjuvant** agent in therapy for **cancer patients**.

Data demonstrating **anti-cancer** or other beneficial effects of melatonin in patients are still limited, but results are encouraging.

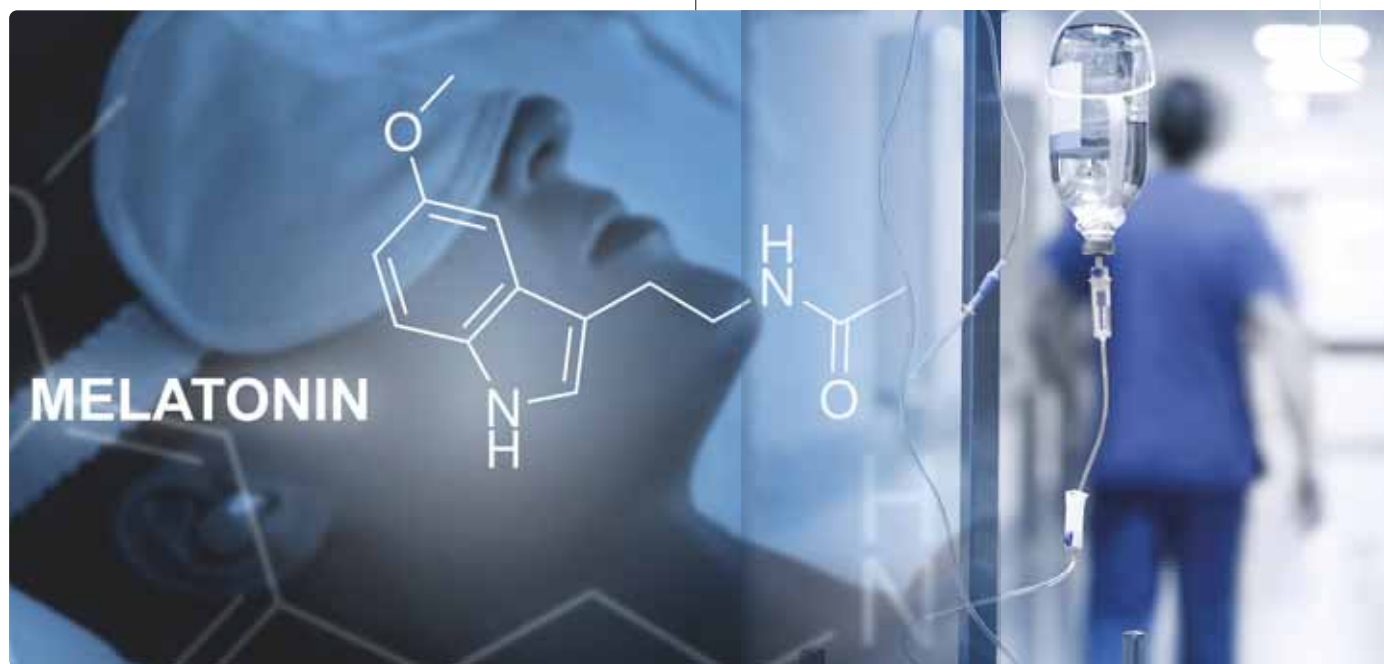
In a handful of completed **clinical trials** in patients with primary brain tumors, colorectal cancer, non-small-cell lung cancer, breast cancer, and brain metastasis, researchers found that **melatonin**, in doses up to **40 mg daily**, worked well with **conventional treatments**.

Researchers also noted improved **quality of life** in cancer patients when no other treatment was available.¹⁰⁻¹⁶

In two separate reviews of clinical trials assessing the use of melatonin during **chemotherapy** or **radiation** for the treatment of solid tumors, **melatonin** was found to **decrease** negative side effects such as fatigue and low platelet counts, **improve** response to treatment, and **increase** one-year survival.^{17,18}

You can access study abstracts about “**melatonin and cancer**” for free on the **National Library of Medicine** website at www.PubMed.gov

At the end of this editorial there is a summary of studies excerpted from the **National Library of Medicine** website about the role of **melatonin** in reducing cancer **incidence** and **mortality**.





Melatonin Use in Rheumatoid Arthritis

By enhancing certain **immune** functions, some early preclinical research suggests melatonin may increase the severity of **rheumatoid arthritis**, which is an autoimmune disease.³³⁻³⁵

This is in contradiction to beneficial effects of melatonin in other **autoimmune** inflammatory diseases.³⁶

Evidence from clinical studies indicates that low-dose melatonin (≤ 10 mg) does not seem to cause harmful effects in subjects with autoimmune diseases, such as multiple sclerosis, ulcerative colitis, lupus, and inflammatory bowel disease.³⁷⁻⁴³

In the past decade, some studies demonstrated that melatonin can alleviate rheumatoid arthritis through the inhibition of specific inflammatory factors.⁴⁴⁻⁴⁸

In fact, a **2021** study found that treatment with **6 mg** of melatonin daily for 12 weeks improved many markers of disease in rheumatoid arthritis patients.⁴⁹

The use of melatonin at doses under **10 mg** in rheumatoid arthritis patients may need consideration by treating physicians.

It is unknown whether high-dose melatonin ≥ 50 mg may exert any harmful effects in those with autoimmune diseases, especially in rheumatoid arthritis patients.



Preclinical Studies on Low- and High-Dose Melatonin

In seeking to ascertain the effects of **high-dose** melatonin we came across some interesting findings suggesting benefits with *higher* dosing. Summaries from these studies are copied below:

- In a mouse model of **amyotrophic lateral sclerosis** (ALS), a **high-dose** oral melatonin delayed disease progression and extended survival.¹⁹
- High-dose melatonin administered intraperitoneally before **myocardial** (heart) injury offered protection against cardiac ischemia-reperfusion injury in Sprague-Dawley rats.²⁰
- High-dose melatonin injected intraperitoneally for 56 days reduced myocardial hypertrophy and preserved **cardiac function** in diabetic Wistar rats.²¹
- High-dose melatonin (human equivalent of **55 mg** a day for 30 days) in **senescence-prone** mice showed that age-related increases in markers of inflammation, oxidative stress and apoptosis were effectively reduced by both low- and high-melatonin doses studied.²²
- Two additional studies with almost identical experimental designs found protective effects of high-dose melatonin on **heart** and **lung** tissue alterations in a mouse model of aging.^{23,24}

Human Studies of High-Dose Melatonin

In a clinical safety study of **ALS** (also called Lou Gehrig's disease) patients, a chronic high dose (**300 mg/day**) of enteral melatonin was well tolerated for up to two years. In this study, a surrogate marker for oxidative stress that is elevated in **ALS** patients was normalized by melatonin treatment. This implies a neuroprotective effect through reduction of oxidative stress.¹⁹

A crossover clinical study including 12 healthy male volunteers investigated the effects of high-dose (**100 mg**) intravenous melatonin and found no adverse effects. This study did not find a greater sedative effect with the **100 mg** intravenous melatonin relative to a **10 mg** dose.²⁵

Indole melatonin (**50 mg**) administered intravenously to three male narcoleptics dramatically increased the amount of REM sleep and decreased REM sleep latency.²⁶

At doses ranging from **10** to **40 mg** daily, melatonin in combination with IL-2 immunotherapy has been shown to improve outcomes in patients being treated for metastatic cancer.²⁷⁻³⁰

A **20 mg** daily oral dose of melatonin, divided into two **10 mg** doses, administered to septic newborns, improved their clinical outcomes after 24 and 48 hours and prevented death. All the newborns treated with melatonin survived, while three of the 10 babies in the non-melatonin group died.³¹

Currently, a clinical trial of antioxidant therapy in adult patients critically ill with septic shock is evaluating the efficacy of a **50 mg** nighttime dose of melatonin. Results are pending (NCT03557229).³²

Short-Term Studies Using High-Dose Melatonin in Humans

A surprising number of **human** studies have been done using varying melatonin doses without serious side effects being found.

In an analysis of 50 studies evaluating the efficacy of oral melatonin supplementation (**1-20 mg**), less than half the studies reported adverse events, which were typically minor and transient. Fatigue was seen most often in studies in which melatonin was taken during daytime hours.⁵⁰

A double-blind, placebo-controlled study evaluating the utility of **5-20 mg** of sublingual melatonin in patients undergoing gynecological surgical procedures reported neither dose-dependent nor dose-independent adverse events.⁵¹

General Safety Data on High-Dose Melatonin

A member of our scientific team did a comprehensive search of the published medical literature. Below is an Executive Summary of this literature review:

Executive Summary: Safety of High-Dose Melatonin

Based on a thorough and comprehensive evaluation of the most up-to-date scientific evidence from reputable sources, the conclusions of our review on efficacy and toxicity/safety of high-dose melatonin are as follows:

-- High-dose melatonin (doses **50 mg** and above) has been used in preclinical and clinical settings, and data collectively show that melatonin even at high doses has a good safety profile and is beneficial, improving disease outcomes.

However, at this time preclinical as well as clinical evidence does not clearly demonstrate that increasing the dose of melatonin is accelerating and/or amplifying melatonin benefits. That is because studies specifically addressing dose-dependent effects of melatonin in various settings are lacking.

-- There are no clinical data showing whether high-dose **50 mg** melatonin may exert any harmful effects in patients with autoimmune diseases, especially rheumatoid arthritis.

-- There is currently no compelling clinical evidence clearly showing that high-dose melatonin (**50 mg** and above) supplementation may interact with prescription drugs and decrease their effectiveness when taken concomitantly.

Oral administration of **1,000 mg a day** of melatonin to five adults for 25 to 30 days resulted in drowsiness being noted as an adverse effect. There were no severe and/or irreversible impacts on clinical parameters (blood pressure, heart rate, ECG, serum chemistry, urine analysis) in these people taking a massive **1,000 mg** dose of melatonin each night for 25 to 30 days.⁵²

Three separate studies did not report adverse side effects using the following **high doses** of melatonin:

- **90 mg**, on average, intravenously administered to healthy patients as well as individuals with seizure disorder and Parkinson's disease,⁵³
- **10 mg** per kilogram (intravenous) in preterm infants and septic neonates,⁵⁴ and
- **100 mg** (intravenous) in healthy subjects.²⁵

These findings suggest that extremely high doses of oral melatonin (**1,000 mg/day**), enteral melatonin (**300 mg/day**) and intravenous melatonin (**1-100 mg**) are safe and do not cause clinically significant side effects.

I am not recommending these high doses, just reporting on what's already been studied in people.

The studies reported in this section were short term and not the long-term, rigorous human trials that the authors of the February 2022 published **JAMA** report¹ and we at **Life Extension** would like to see conducted.

The dilemma is who is going to pay for a multimillion-dollar, long-term clinical trial using high-dose melatonin when it has been available as a low-cost dietary supplement for the last 30 years?

High-Dose Melatonin and Prescription Drugs

There is currently no compelling clinical evidence clearly showing that high-dose melatonin (**30-50 mg**) supplementation will interact with prescription drugs and decrease their effectiveness when taken concomitantly.

The comprehensive 2019 review of 50 studies described earlier including 17 studies in which participants were taking a variety of common medications or receiving treatment for cancer, did not find reports of apparent drug interactions.⁵⁰

The caveat, however, is that there are relatively little human data enabling us to know this for certain.



My only concern is for those with a propensity for low blood pressure, especially because blood pressure normally drops lower at night.

Melatonin has beneficial blood pressure-lowering effects.⁵⁵⁻⁵⁷

Those with **high blood pressure** often take their **anti-hypertensive drug(s)** at night for maximal efficacy. Melatonin may provide additional blood pressure-reducing effects, especially for those challenged to achieve optimal blood pressure levels.

Those concerned with **blood pressure** dropping too low, but who still want to try *higher*-dose melatonin, may consider starting with perhaps **6-10 mg** a night, using an at-home monitor to **self-assess blood pressure**, and adjusting the melatonin dose upwards if **blood pressure** does not drop too low.

I hope every one of our readers has an **at-home blood pressure monitor**, whose prices continue to drop to an affordable range.

The **30-50 mg** nightly doses of **melatonin** I have taken over the past two years have not caused any apparent side effects in me.

Some of you who do not rapidly metabolize melatonin will likely face next-day grogginess and may not want to take this **high** melatonin dose.

Melatonin Put Life Extension® on the Map

When **Life Extension®** introduced **melatonin** to the world in **1992**, virtually no one had ever heard the term. It's now a household name liberally described in the mainstream media as facilitating better sleep.

When the **New York Academy of Sciences** published a book on the multiple benefits of **melatonin**, the media picked up on it and I became a guest on some of the most popular talk shows in America.

The **JAMA** report (**February 1, 2022**) warns about unknown risks of long-term “self-administered” melatonin. **JAMA** is the **American Medical Association’s** most widely read journal.

Contrary to the position taken in the **JAMA** report, I present published data in this editorial as to why I am self-experimenting with *higher-dose melatonin*.

In particular, I am intrigued by the consistency of data indicating that melatonin may reduce **cancer risk** and improve outcomes of cancer patients treated with conventional therapy. These findings, which you can read for yourself at www.PubMed.gov, provide a compelling reason for most aging humans to supplement with at least a few milligrams of melatonin each night.

Copied at the end of this article are the results of a recent database search using the terms “**melatonin and cancer**.”

Those who self-experiment as I do may consider trying **10 mg** or more of melatonin about 30 minutes before bedtime. I started off with **10 mg** and added some sustained-release melatonin so as not to wake up too early. My average nightly melatonin dose now is around **20 mg**.

In this month’s issue...

The world has woken up to the fact that normal **aging** is accompanied by loss of **immune** functions. The article on page 32 describes the immune enhancing properties of specific **mushrooms**.

Vitamin K helps maintain **bone density** and protect against soft tissue calcification. The article on page 50 reviews research showing how vitamin K can improve **heart** health.

Other articles this month describe the *systemic* effects of **N-aceyl-L-cysteine** and a popular way people today are taking their nightly **melatonin**.

For longer life,



William Faloon, Co-Founder
Life Extension®



Our Ongoing Support of Biomedical Research

Life Extension® donates supplements to physician-scientists who use them in **clinical trials** to ascertain efficacy against a wide range of degenerative disorders.

In **2021**, a study was published using **20 mg melatonin** capsules that **Life Extension®** specially formulated to study on non-small-cell **lung cancer** patients. We also provided identical-looking **placebo** capsules for this outside research group.

The data below highlight the **improved survival** in those receiving **20 mg of melatonin** compared to **placebo**:

DAILY EVENING MELATONIN PROLONGS SURVIVAL AMONG PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER¹⁰

- **20 mg** melatonin as an adjunctive to standard chemo treatment.
- Evening supplementation of melatonin reduced risk of death by **39%**.
- Individuals with normal baseline sleep had a median survival of **17.6 months** with evening **melatonin** compared to **10.4 months** in the **placebo** group.

Acknowledgments: We would like to thank William Faloon of **Life Extension** for providing melatonin and placebo for this study.

Biological Rhythm Research. 2021:1-15.

National Library of Medicine Titles and Descriptions of Published Studies About Melatonin and Cancer

These pages contain titles and brief descriptions of studies that were published in **2021** and **2022**, listed on the federal government's National Library of Medicine's data base (www.pubmed.gov).

What we reprinted is only a small portion of the hundreds of studies about "**melatonin and cancer**" one can easily access by logging on to www.PubMed.gov

Melatonin in Cancer Treatment: Current Knowledge and Future Opportunities.

Talib WH, Alsayed AR, Abuawad A, Daoud S, Mahmud AI.

Molecules. 2021 Apr 25;26(9):2506. doi: 10.3390/molecules26092506.PMID: 33923028 **Free PMC article**. [Review](#).

Epidemiological and experimental studies have documented that melatonin could inhibit different types of cancer in vitro and in vivo. ...Studies discussed in this review will provide a solid foundation for researchers and physicians to design and develop new...

Melatonin-A New Prospect in Prostate and Breast Cancer Management.

Anim-Koranteng C, Shah HE, Bhawnani N, Ethirajulu A, Alkasabera A, Onyali CB, Mostafa JA.

Cureus. 2021 Sep 20;13(9):e18124. doi: 10.7759/cureus.18124. eCollection 2021 Sep.PMID: 34692334 **Free PMC article**. [Review](#).

Melatonin exerts its oncostatic effect by inhibiting angiogenesis, preventing cancer spread and growth, and improving the sensitivity of cancer cells to radiation and chemotherapy in both prostate and breast cancer. This review aims to highlight some...

Circadian Rhythm and Concentration of Melatonin in Breast Cancer Patients.

Ahabrach H, El Mlili N, Errami M, Cauli O.

Endocr Metab Immune Disord Drug Targets. 2021;21(10):1869-1881. doi: 10.2174/1871530320666201201110807.PMID: 33261546 [Review](#).

Melatonin has also been shown to display anti-proliferative effects on breast cancer growth and proliferation. ...CONCLUSION: Circadian rhythm and the concentration of melatonin in the blood are altered in patients with breast cancers, and it can...

Melatonin and Pathological Cell Interactions: Mitochondrial Glucose Processing in Cancer Cells.

Reiter RJ, Sharma R, Rosales-Corral S, Manucha W, Chuffa LGA, Zuccari DAPC.

Int J Mol Sci. 2021 Nov 19;22(22):12494. doi: 10.3390/ijms222212494.PMID: 34830375 **Free PMC article**. [Review](#).

Melatonin is synthesized in the pineal gland at night. Since melatonin is produced in the mitochondria of all other cells in a non-circadian manner, the amount synthesized by the pineal gland is less than 5% of the total. Melatonin produced in mitochondria in ...

Usefulness of Melatonin and Other Compounds as Antioxidants and Epidrugs in the Treatment of Head and Neck Cancer.

Guerra J, Devesa J.

Antioxidants (Basel). 2021 Dec 24;11(1):35. doi: 10.3390/antiox11010035.PMID: 35052539 **Free PMC article**. [Review](#).

Along with genetic mutations, aberrant epigenetic alterations are the initiators of head and neck cancer carcinogenesis. Currently, several drugs are being developed to correct these epigenetic alterations, known as epidrugs. ...The objective of this review is to describe ...

Sleep disorders and cancer: State of the art and future perspectives.

Mogavero MP, DelRosso LM, Fanfulla F, Bruni O, Ferri R.

Sleep Med Rev. 2021 Apr;56:101409. doi: 10.1016/j.smrv.2020.101409. Epub 2020 Nov 28.PMID: 33333427 [Review](#).

A bidirectional connection between sleep and cancer exists; however, the specific associations between individual sleep disorders and particular tumors are not very clear. An accurate assessment of sleep disorders in cancer patients is necessary to improve patient ...

Involvement of NRF2 in Breast Cancer and Possible Therapeutical Role of Polyphenols and Melatonin.

Tascioglu Aliyev A, Panieri E, Stepanić V, Gurer-Orhan H, Saso L.

Molecules. 2021 Mar 25;26(7):1853. doi: 10.3390/molecules26071853.PMID: 33805996 **Free PMC article**. [Review](#).

Due to its regulatory role in the expression of numerous cytoprotective genes involved in the antioxidant and anti-inflammatory responses, the modulation of NRF2 seems to be a promising approach in the prevention ...

Role and Therapeutic Potential of Melatonin in Various Type of Cancers.

Gurunathan S, Qasim M, Kang MH, Kim JH.

Onco Targets Ther. 2021 Mar 18;14:2019-2052. doi: 10.2147/OTT.S298512. eCollection 2021. PMID: 33776451 Free PMC article. Review.

Lung, prostate, colorectal, stomach, and liver cancers are the most common types of cancer in men, whereas breast, colorectal, lung, cervical, and thyroid cancers are the most common among women. ...The combination of melatonin with conventional drugs ...

The effect of melatonin on sleep quality and insomnia in patients with cancer: a systematic review study.

Jafari-Koulaee A, Bagheri-Nesami M.

Sleep Med. 2021 Jun;82:96-103. doi: 10.1016/j.sleep.2021.03.040. Epub 2021 Apr 25. PMID: 33910162 Review.

Therefore, the aim of the present systematic review was to investigate effect of melatonin on sleep quality and insomnia in patients with cancer. METHODS: The present systematic review was conducted in 2021. ...CONCLUSIONS: The present review study showed that melatonin may be ...

Pan-cancer analyses reveal genomics and clinical characteristics of the melatonergic regulators in cancer.

Zhang J, Jiang H, Du K, Xie T, Wang B, Chen C, Reiter RJ, Cen B, Yuan Y.

J Pineal Res. 2021 Oct;71(3):e12758. doi: 10.1111/jpi.12758. Epub 2021 Sep 5. PMID: 34289167

Melatonin, an endogenous hormone, plays protective roles in cancer. ...In the present study, we performed a comprehensive characterization of melatonin regulators in 9,125 tumor samples across 33 cancer types using multi-omic data from The Cancer Genome Atlas ...

Melatonin inhibits proliferation and viability and promotes apoptosis in colorectal cancer cells via upregulation of the microRNA-34a/449a cluster.

Ji G, Zhou W, Li X, Du J, Li X, Hao H.

Mol Med Rep. 2021 Mar;23(3):187. doi: 10.3892/mmr.2021.11826. Epub 2021 Jan 5. PMID: 33398374 Free PMC article.

Melatonin exerts anticarcinogenic effects via various mechanisms; however, the identified underlying molecular mechanisms do not explain the full breadth of anti-CRC effects mediated by melatonin. ...Therefore, melatonin may serve as a potential therapeutic ...

A New Paradigm in the Relationship between Melatonin and Breast Cancer: Gut Microbiota Identified as a Potential Regulatory Agent.

Laborda-Illanes A, Sánchez-Alcoholado L, Boutriq S, Plaza-Andrades I, Peralta-Linero J, Alba E, González-González A, Queipo-Ortuño MI.

Cancers (Basel). 2021 Jun 23;13(13):3141. doi: 10.3390/cancers13133141. PMID: 34201776 Free PMC article. Review.

In this review we summarize a possible connection between gut microbiota, melatonin production, and breast cancer. An imbalance in gut bacterial population composition (dysbiosis), or changes in the production of melatonin (circadian disruption) alters ...

The Intricate Relationship between Melatonin and Breast Cancer: A Short Review.

Pistioli L, Katsarelis D, Audisio RA, Olofsson Bagge R.

Chirurgia (Bucur). 2021 Mar-Apr;116(2 Suppl):24-34. PMID: 33963691 Free article.

There is ongoing research investigating the deterrent relationship between melatonin and malignancies and in particular breast cancer. The aim of this article is to review some of the most important findings concerning the effect of melatonin on cancer ...

Melatonin and its derivative disrupt cancer stem-like phenotypes of lung cancer cells via AKT downregulation.

Phiboonchaiyanan PP, Puthongking P, Chawjarean V, Harikarnpakdee S, Sukprasansap M, Chanvorachote P, Pripem A, Govitrapong P.

Clin Exp Pharmacol Physiol. 2021 Dec;48(12):1712-1723. doi: 10.1111/1440-1681.13572. Epub 2021 Aug 31. PMID: 34396568

Cancer stem cells (CSCs), a small subpopulation of tumour cells, have properties of self-renewal and multipotency, which drive cancer progression and resistance to current treatments. Compounds potentially targeting CSCs have been recently developed. This study show ...

Melatonin and Cancer: A Polyhedral Network Where the Source Matters.

Bonmati-Carrion MA, Tomas-Loba A.

Antioxidants (Basel). 2021 Feb 1;10(2):210. doi: 10.3390/antiox10020210. PMID: 33535472 Free PMC article. Review.

Indeed, this activity has been demonstrated to be mediated by interfering with various **cancer** hallmarks, and different epidemiological studies have also linked light at night (**melatonin** suppression) with a higher incidence of different types of **cancer**.

Melatonin interrupts osteoclast functioning and suppresses tumor-secreted RANKL expression: implications for bone metastases.

Liu PI, Chang AC, Lai JL, Lin TH, Tsai CH, Chen PC, Jiang YJ, Lin LW, Huang WC, Yang SF, Tang CH.

Oncogene. 2021 Feb;40(8):1503-1515. doi: 10.1038/s41388-020-01613-4. Epub 2021 Jan 15. PMID: 33452455

We also observed that melatonin inhibits RANKL production in lung and prostate cancer cells by downregulating the p38 MAPK pathway, which in turn prevents cancer-associated osteoclast differentiation. ...These findings show promise for melatonin in the ...

Melatonin inhibits lung cancer development by reversing the Warburg effect via stimulating the SIRT3/PDH axis.

Chen X, Hao B, Li D, Reiter RJ, Bai Y, Abay B, Chen G, Lin S, Zheng T, Ren Y, Xu X, Li M, Fan L.

J Pineal Res. 2021 Sep;71(2):e12755. doi: 10.1111/jpi.12755. Epub 2021 Jul 30. PMID: 34214200

Recently, the morbidity and mortality from lung cancer have continued to increase. Mitochondrial dysfunction plays a key role in apoptosis, proliferation, and the bioenergetic reprogramming of cancer cells, especially for energy metabolism. Herein, we investigated ...

Effects of melatonin and doxorubicin on primary tumor and metastasis in breast cancer model.

Tanriover G, Dilmac S, Aytac G, Farooqi AA, Sindel M.

Anticancer Agents Med Chem. 2021 Dec 12. doi: 10.2174/1871520621666211213094258. Online ahead of print. PMID: 34961467

BACKGROUND: Melatonin exerts oncostatic effects on breast cancer via immunomodulation and anti-oxidation. ...Based on these results, melatonin is a promising candidate for combinatory use with conventional chemotherapeutics for breast cancer treatment. ...

MT1 and MT2 melatonin receptors play opposite roles in brain cancer progression.

Kinker GS, Ostrowski LH, Ribeiro PAC, Chanoch R, Muxel SM, Tirosh I, Spadoni G, Rivara S, Martins VR, Santos TG, Markus RP, Fernandes PA.

J Mol Med (Berl). 2021 Feb;99(2):289-301. doi: 10.1007/s00109-020-02023-5. Epub 2021 Jan 3. PMID: 33392634

Primary brain tumors remain among the deadliest of all cancers. Glioma grade IV (glioblastoma), the most common and malignant type of brain cancer, is associated with a 5-year survival rate of < 5%. ...However, our understanding of the specific effects mediated ...

Melatonin inhibits gallbladder cancer cell migration and invasion via ERK-mediated induction of epithelial-to-mesenchymal transition.

Tang H, Shi X, Zhu P, Guo W, Li J, Yan B, Zhang S.

Oncol Lett. 2021 Aug;22(2):609. doi: 10.3892/ol.2021.12870. Epub 2021 Jun 15. PMID: 34188711 Free PMC article.

However, little is known regarding the effects of melatonin on gallbladder cancer (GBC) cells. The present study aimed to investigate the role of melatonin on the prevention of GBC cell invasion. ...Thus, melatonin may be used as a potential novel ...

Melatonin indirectly decreases gastric cancer cell proliferation and invasion via effects on cancer-associated fibroblasts.

Liu D, Shi K, Fu M, Chen F.

Life Sci. 2021 Jul 15;277:119497. doi: 10.1016/j.lfs.2021.119497. Epub 2021 Apr 18. PMID: 33864820

Recent studies have revealed the potential value of melatonin in cancer therapy, but its role in gastric cancer and CAFs requires further exploration. ...SIGNIFICANCE: This study provides insights into the role of melatonin in the tumor microenvironment ...

Alcohol and melatonin.

Kurhaluk N.

Chronobiol Int. 2021 Jun;38(6):785-800. doi: 10.1080/07420528.2021.1899198. Epub 2021 Mar 24. PMID: 33761823 Review.

It discusses the main clinical effects of melatonin on alcohol injury and the main targets as a therapy for alcohol disorders. Chronobiological effects of ethanol are related to melatonin suppression that has been associated with, among others, cancer risk ...

Melatonin reduces proliferation and promotes apoptosis of bladder cancer cells by suppressing O-GlcNAcylation of cyclin-dependent-like kinase 5.

Wu J, Tan Z, Li H, Lin M, Jiang Y, Liang L, Ma Q, Gou J, Ning L, Li X, Guan F.

J Pineal Res. 2021 Oct;71(3):e12765. doi: 10.1111/jpi.12765. Epub 2021 Sep 18. PMID: 34487576

Dysregulated glycosylation, particularly O-GlcNAcylation, is often a biomarker of cancer cells. In this study, elevated O-GlcNAc level in bladder cancer was inhibited by melatonin treatment. Melatonin treatment inhibited proliferation and migration and ...

Associations between artificial light at night and risk for thyroid cancer: A large US cohort study.

Zhang D, Jones RR, James P, Kitahara CM, Xiao Q.

Cancer. 2021 May 1;127(9):1448-1458. doi: 10.1002/cncr.33392. Epub 2021 Feb 8. PMID: 33554351

BACKGROUND: Light at night (LAN) inhibits nighttime secretion of melatonin and may cause circadian disruption, which may be a risk factor for cancer. Recent studies have linked high LAN exposure with elevated breast cancer risk. Given that breast cancer ...

Melatonin Targets Metabolism in Head and Neck Cancer Cells by Regulating Mitochondrial Structure and Function.

Guerra-Librero A, Fernandez-Gil BI, Florido J, Martinez-Ruiz L, Rodríguez-Santana C, Shen YQ, García-Verdugo JM, López-Rodríguez A, Rusanova I, Quiñones-Hinojosa A, Acuña-Castroviejo D, Marruecos J, De Haro T, Escames G.

Antioxidants (Basel). 2021 Apr 14;10(4):603. doi: 10.3390/antiox10040603. PMID: 33919790 Free PMC article.

In this study, we aim to investigate the role of melatonin in mitochondrial metabolism and its functional consequences in head and neck cancer. ...Our findings highlight new molecular pathways involved in melatonin's oncostatic activity, suggesting ...

Melatonin Inhibits Migration and Invasion in LPS-Stimulated and -Unstimulated Prostate Cancer Cells Through Blocking Multiple EMT-Relative Pathways.

Tian QX, Zhang ZH, Ye QL, Xu S, Hong Q, Xing WY, Chen L, Yu DX, Xu DX, Xie DD.

J Inflamm Res. 2021 May 25;14:2253-2265. doi: 10.2147/JIR.S305450. eCollection 2021. PMID: 34079331 Free PMC article.

PURPOSE: Gram-negative bacteria are usually found in prostate cancer (PCa) tissues. This study aims to investigate the role of lipopolysaccharide (LPS), a glycolipid compound found in the outer membrane of gram-negative bacteria, on the migration and invasion of PCa cells, ...



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(References continued on page 18.)

National Library of Medicine

Back in the **1980s**, finding **medical studies** was an arduous task.

To uncover published data, our group spent days in **medical libraries** using an archaic paper system (Index Medicus) to find relevant medical journals.

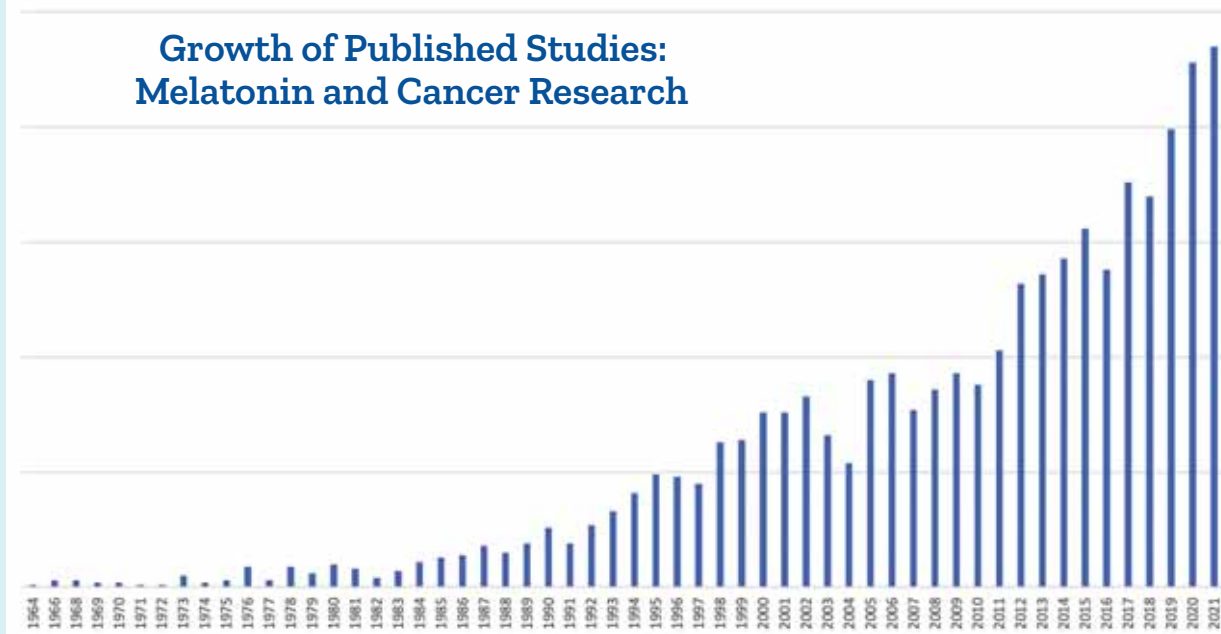
We then had to hope the library subscribed to that journal, photocopy relevant articles, bring them back to our office and mail information to others for further analysis.

In the early **1990s**, a subscription service became available whereby I received four large floppy disks with new medical studies every Saturday. I would load the disks onto my computer and search items of interest. This was a huge **improvement** compared to spending days at a **medical library**.

Then in **1997** the **National Library of Medicine** offered **free** public access to medical articles dating back to the late 1970s. The **National Library of Medicine** is operated by the United States government and is the world's largest medical library.

This free service not only makes my work more efficient but enables anyone who reads **Life Extension Magazine®** to check out studies we write about and find out as many details as they'd like.

Growth of Published Studies: Melatonin and Cancer Research



This chart shows the surging numbers of published studies at www.PubMed.gov when entering the search phrase: **"melatonin and cancer"**

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MJ

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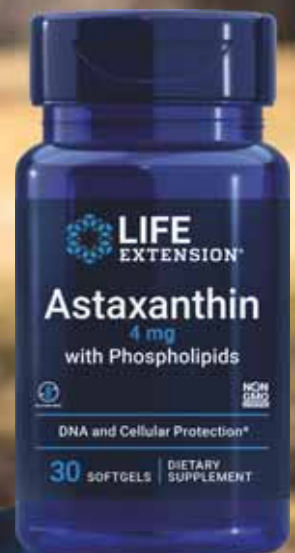
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Life Extension® combines **4 mg** of **astaxanthin** with a blend of four different **phospholipids**, which has been shown to enhance carotenoid **absorption** by **several-fold**.⁴

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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.

Actiponin® is a trademark of TG Biotech Co., Ltd.



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For full product description and to order **AMPK Metabolic Activator**, call **1-800-544-4440** or visit **www.LifeExtension.com**

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3 mg of melatonin per 1 mL dropper (approximately 20 drops).

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PRICE: \$9



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In the News



Fish Oil Lowers Risk of Liver Cancer

A study published in *Frontiers in Nutrition* found a significantly lower risk of liver cancer among people who supplemented with fish oil, compared to those who didn't.*

The study included 434,584 middle-aged and older men and women enrolled in the UK Biobank who were cancer free on enrollment.

The median follow-up period of this large study group was **7.8 years**.

Compared to people who did not use **fish oil**, those who supplemented with fish oil had a **44% lower** risk of liver cancer, a **52% lower** risk of hepatocellular carcinoma, and a **40%** lower risk of intrahepatic cholangiocarcinoma.

Editor's Note: "The inverse association of fish-oil use with the risk of total liver cancer did not vary by baseline age, sex, smoking status, or diabetes of the participants," the researchers stated.

* *Front Nutr.* 2021 Dec 31;8:771984.

Curcumin Can Help People with Diabetic Kidney Disease

Diabetic kidney disease is a common microvascular complication of diabetes.

A study published in the journal *Evidence-Based Complementary and Alternative Medicine* reported an **improvement** in response to **curcumin** supplementation.*

People with kidney disease have a *higher* risk for cardiovascular morbidity and mortality, which are closely associated with risk factors such as hypertension and chronic inflammation.

A meta-analysis of five randomized, double-blind, placebo-controlled clinical trials, including 290 individuals with diabetic kidney disease, concluded that **curcumin** supplementation was associated with improved **creatinine** (a marker of kidney function), cholesterol, glucose and systolic blood pressure, compared to a **placebo**.

Editor's Note: "Up to 40% of patients with type II diabetes develop DKD, and DKD is currently the leading cause of end-stage renal disease worldwide," the authors stated.

* *Evid Based Complement Alternat Med.* 2021 Dec 2;2021:6109406.





Supplementing with Zinc Linked to Lower Risk of Alzheimer's Disease

A study published in the *Journal of Neuroscience* found an association between **zinc** supplementation and a decreased risk of Alzheimer's disease as well as a reduction in the progression of cognitive decline in Alzheimer's disease patients.*

Researchers utilized data from the Alzheimer's Disease Neuroimaging Initiative database, which included 1,631 individuals who were cognitively normal or diagnosed with mild cognitive impairment or early Alzheimer's disease.

Subjects were evaluated upon enrollment, at six and 12 months, and yearly thereafter, during up to 10 years of follow-up.

Among those who reported supplementing with zinc, **6%** were diagnosed with Alzheimer's disease compared to **26%** of those who reported no zinc supplement use.

Editor's Note: "Here we provide epidemiological evidence suggesting that zinc supplementation was associated with reduced risk and slower cognitive decline in people with Alzheimer's disease and mild cognitive impairment," the authors stated.

* *J Neurosci.* 2021 Mar 31;41(13):3025-3038.

Better Bone Health with Collagen Peptides

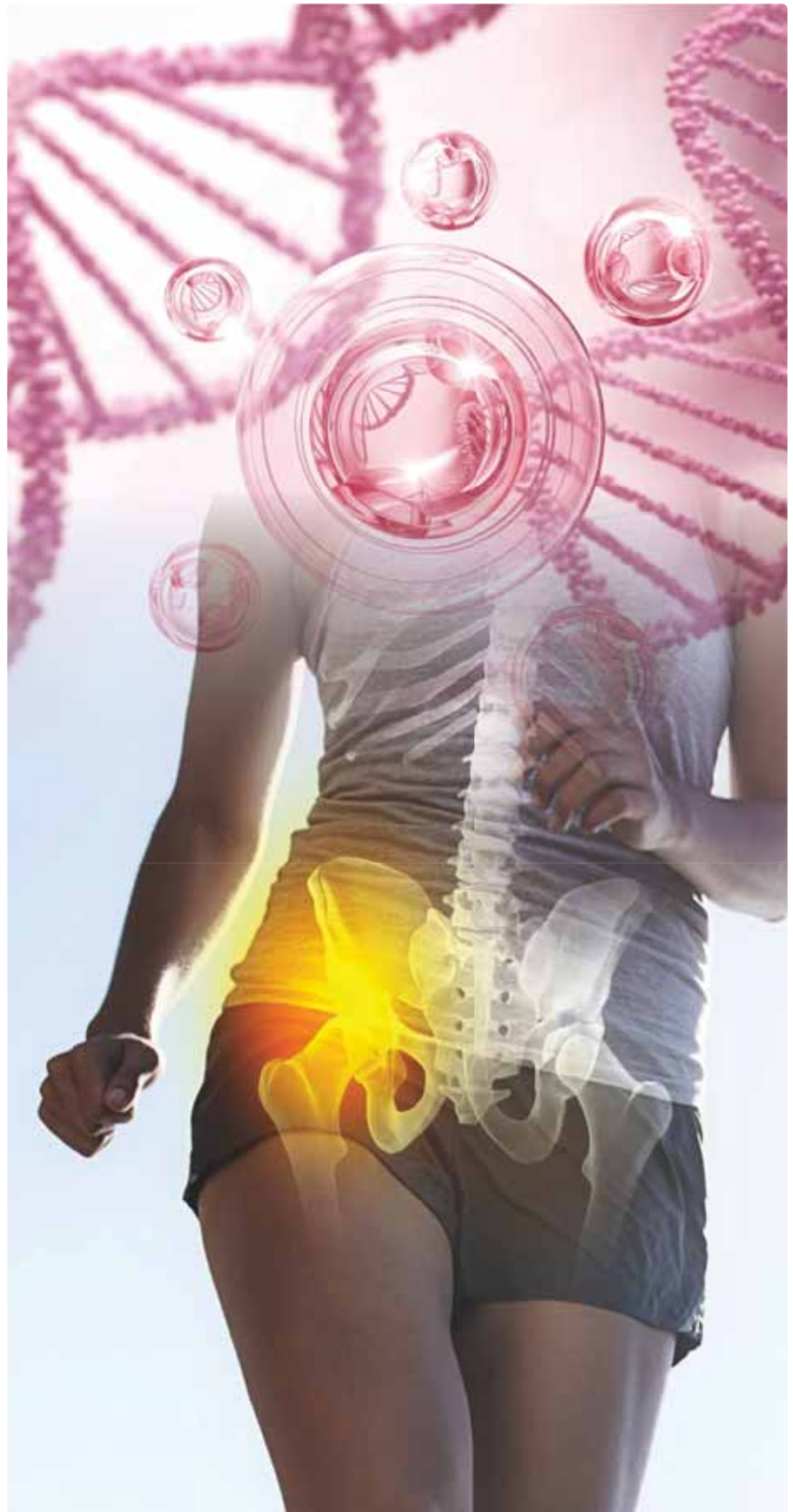
The addition of collagen peptides, the building blocks of collagen, to a bone-supporting regimen of calcium and vitamin D was associated with greater improvements in measures of bone health compared to calcium and vitamin D alone, according to a study published in the *Journal of Clinical Densitometry*.*

The study included 51 postmenopausal women with osteopenia, a condition of lower-than-normal bone mineral density that is associated with an increased risk of developing osteoporosis. All participants received **500 mg** of calcium and **400 IU** of vitamin D3 daily for one year. Twenty-three women also received **5 grams** of collagen peptides.

After one year, women who received **collagen** peptides had a significant increase in bone mineral content and volumetric bone mineral density in trabecular (porous) bone tissue of the tibia, compared to values measured at the beginning of the study, and compared to participants who received calcium and vitamin D alone.

Editor's Note: Volumetric bone mineral density also improved in cortical (more solid) bone among collagen peptides-supplemented participants in comparison with those who did not receive collagen.

* *J Clin Densitom.* 2021 Nov 25;S1094-6950(21)00099-8.



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MUSHROOMS

That *Boost*

IMMUNE FUNCTION

BY MICHAEL DOWNEY

Mushrooms have been used medicinally for *thousands* of years.¹

Modern science has pinpointed a primary reason:

They contain beneficial compounds called **beta glucans** that *boost immune function*.²⁻⁵

On their own, **beta glucans** deliver **antiviral** and **immunity-strengthening** properties.²⁻⁵

In **human** studies, taking **beta glucans** reduces the length and severity of **upper respiratory tract infections** such as the common **cold** and **flu**.⁶⁻¹¹

Combining beta glucans with medicinal mushrooms may supercharge a variety of **immune functions**.

What Are Beta Glucans?

Beta glucans are a group of polysaccharides found in the cell walls of **mushrooms**, seaweed, and whole grains.⁷

Beta glucans derived from yeast and fungi are known for their **immunomodulating** properties.⁷

They also help nourish the gut microbiota and augment the action of **immune cells**.^{3,12-15}

Key Immune-Supportive Mushrooms

There are hundreds of strains of mushrooms. **Three** that most effectively support the immune system are **shiitake**, **maitake**, and **chaga**.

SHIITAKE

Shiitake mushrooms have long been used in traditional Asian medicine.¹⁶ They *increase* the number of immune cells, including **T-cells**, which fight specific kinds of viruses, and **NK (natural killer) cells**, which kill a variety of virally infected cells and tumors.¹⁷

In cell studies **shiitake extract** was able to directly inactivate several types of **viruses** and block viral replication.¹⁸⁻²⁰

In an animal model of severe **bacterial lung infection**, shiitake mushrooms significantly *decreased* the number of bacteria in the lungs and improved the animals' condition.²¹

Shiitake also boosts secretion of **antibodies** that protect the digestive tract and reduces **C-reactive protein**, a marker of **inflammation**.¹⁷

MAITAKE

Commonly used in cuisine, **maitake** mushrooms were shown in preclinical studies to activate some of the *first* immune cells to fight an infection, including **NK cells** and **macrophages**.^{22,23}

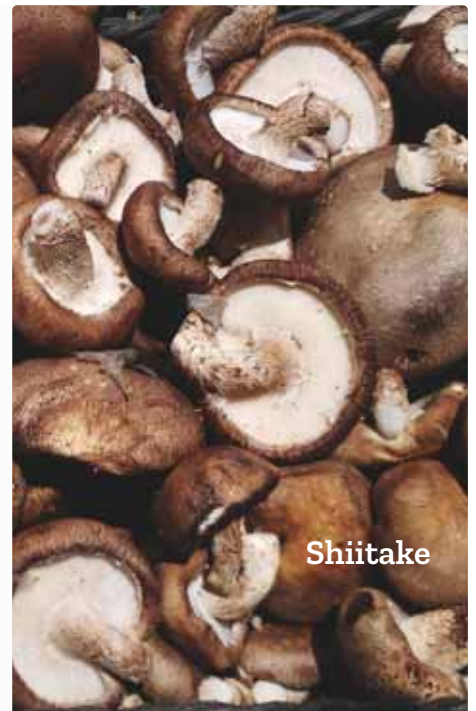
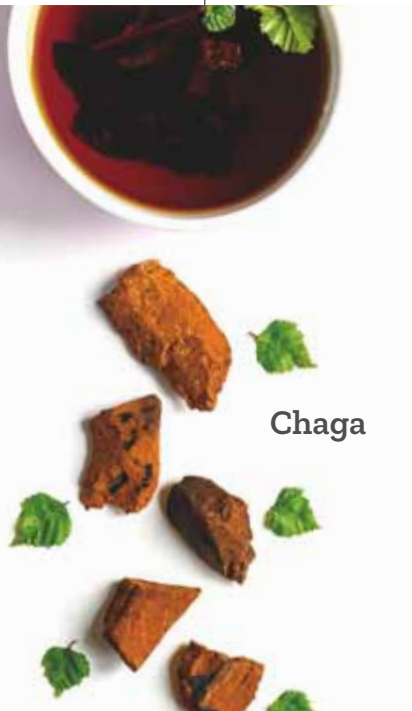
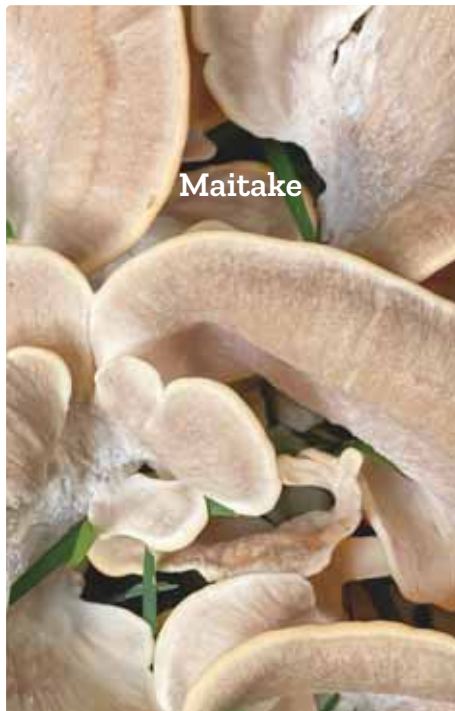
Extracts of maitake also induce the secretion of **interferons**, proteins that improve the body's ability to defend against infection.²³

CHAGA

Chaga mushrooms, which grow on alder, beech, birch, and various other hardwood trees, are powerful **immuno-modulators**.

When scientists treated mice with a drug that *inhibits* **immune system** activity, chaga extract returned levels of immune cells almost back to normal. It also kept down levels of **tumor necrosis factor**, a marker of inflammation.²⁴

In preclinical studies, chaga demonstrated **antiviral** activity against a wide range of viruses, including influenza, herpes, hepatitis C, HIV, and others.²⁵





WHAT
YOU
NEED
TO
KNOW

Mushrooms and Beta Glucans Boost Immunity

Activating the Immune System

Mushrooms contain numerous health-promoting compounds. But perhaps the most powerful and bioactive immune supporters are **beta glucans**.

Beta glucans bind to receptors found on an assortment of cells important for **immunity**.^{3,26} This boosts the function of these cells, helping them defend against infection and other threats.

Immune responses can be divided into two types:²⁷

- **Innate immunity**, which forms the body's first line of defense, is accomplished by immune cells including macrophages, neutrophils, and NK cells.
- **Adaptive immunity** cells include lymphocytes, such as B-cells and T-cells. These are the specialists brought in later to fight off *specific* threats, like a particular bacteria or virus. Adaptive immunity helps the body develop **long-term immunity** to a pathogen.

Beta glucans activate and stimulate **both** systems.^{3,4,17,28,29}

- **Mushrooms** have long been used for medicinal properties. **Shiitake**, **maitake**, and **chaga** mushrooms help support the immune system, activating immune cells.
- **Beta glucans**, compounds found in the cell walls of mushrooms, contribute to these **immune** benefits.
- Oral intake of **beta glucans** can boost the immune system's ability to prevent and fend off **infections** (including the common cold and flu), and support a healthy gut microbiota, and it may reverse age-related weakening of the immune system.
- Blending **beta glucans** with **shiitake**, **maitake**, and **chaga** mushrooms may help optimize healthy immune function.



Results of Human Tests

To validate these benefits in **humans**, scientists conducted a number of different trials. Volunteers were randomized to receive either a **placebo** or **beta glucans**. Most of these studies used a **250 mg** dose of beta-glucans.⁶⁻¹¹

Beta glucans demonstrated infection-fighting effects, particularly in **upper respiratory tract infections** such as the common **cold** and **flu**.

Participants who received **beta glucans** had:⁶⁻¹¹

- Fewer symptomatic days,
- Less severe infection symptoms,
- Fewer workdays lost to illness,
- Increased numbers of immune cells in the blood,
- Higher levels of interferon secretion, and
- Increased secretion of **antibodies** in the saliva, a defense against digestive tract and respiratory tract infections.

Higher Mushroom Intake Associated with Reduced Mortality

In September 2021, scientists with the College of Medicine at **Pennsylvania State University** published results from a meta-analysis of prospective studies that included over 600,000 individuals, on the relationship between **mushroom intake** and **mortality**.³⁴

They found that *higher* mushroom consumption correlated with a *lower* risk of **death from any cause**.

This study had several major strengths, including the facts that it involved a very comprehensive meta-analysis and it employed a sample that was nationally representative of the American adult population.

An earlier study by the same team, with **15,546** participants followed for an average of nearly 20 years, from the Third National Health and Nutrition Examination Survey (NHANES III), found an even stronger correlation between mushroom intake and **lower all-cause mortality**.³⁵

In a different meta-analysis, researchers found that higher mushroom consumption was associated with a *lower* risk of **cancer**.³⁶

When site-specific cancer was studied, a significant association was observed with reduced **breast cancer** risk and greater mushroom consumption.³⁶

Beta glucans can improve immune responses to *other* challenges as well. One study looked at **ragweed allergy** sufferers who received either a placebo or **250 mg of beta glucans**.³⁰

After four weeks, those receiving **beta glucans** had significant *reductions* in total allergy symptoms and severity. Measures of mood, energy, vigor, sleep, and overall quality of life were all improved.³⁰

Reversing Immune Senescence

The elderly become more susceptible to infectious diseases and cancer due to a deterioration of immune function known as **immunosenescence**.³¹

In animal models of aging, intake of **beta glucans** can help *prevent* or even *reverse* this weakening of the immune system.^{28,32}

In one mouse study, **beta glucans** boosted the numbers of immune cells, *and* improved their function, which had a **rejuvenating effect** on immune system responses.³²

Stronger Gut Defenses

The **gut microbiota** is made up of the trillions of microorganisms in the digestive tract. Beneficial populations of these microorganisms are critical to fighting **infections** and maintaining optimal overall health.

Both **mushrooms** and isolated **beta glucans** encourage the growth of healthy microbiota.^{3,13-15}

The benefits don't stop there. When beneficial bacteria consume beta glucans, they produce **short-chain fatty acids** as a byproduct.^{13,15} Among other benefits, these fatty acids:³³

- Reduce harmful **inflammation**,
- Support a healthy gut lining,
- Defend against **cancer**, and
- Help regulate appetite and metabolism.

Combining **beta glucans** with immune-supporting **mushrooms** may help maximize the function of the immune system.

Summary

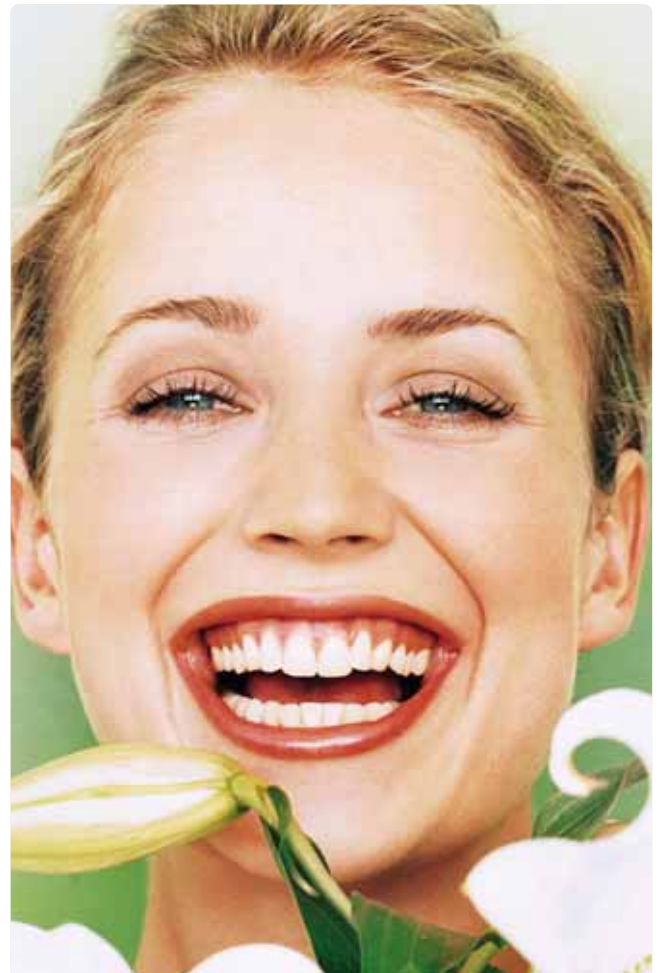
Mushrooms have wide-ranging medicinal properties, including powerful support for the function of the **immune system**.

Beta glucans are compounds found in the cell walls of mushrooms, and in yeast, seaweed, and some grains that are also known to help the immune system.

Beta-glucans have been shown to improve immune responses, helping to:

- Prevent and fight **infections** like the common cold and flu,
- Prevent or reverse immune senescence, and
- Support a healthy gut microbiota.

A carefully formulated blend of **beta glucans** from yeast as well as **shiitake**, **maitake**, and **chaga mushrooms** can help support healthy immune function. •



If you have any questions on the scientific content of this article, please call a **Life Extension Wellness Specialist** at 1-866-864-3027.

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A *NEW* Way to Enjoy **MELATONIN**

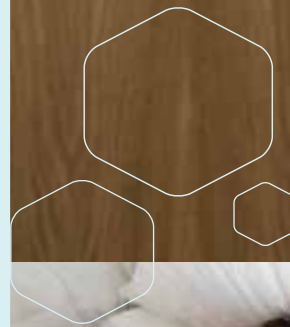
BY MICHAEL DOWNEY

Melatonin has helped many people sleep better.¹

But not all those who suffer **sleep issues** derive perceivable **benefits**.

A delicious *new* way to boost **individualized melatonin** levels is available in the form of a vegetarian, *sugar-free gummy*.

This article describes how melatonin functions to improve sleep and how you may better derive these benefits.



The Dangers of Inadequate Sleep

Getting **too little sleep** doesn't just leave people fatigued. **Inadequate sleep** is associated with increased risk of:^{2,3}

- Excess body weight and obesity,
- Type II diabetes,
- Sleep apnea,
- Hypertension,
- Mood disorders (depression, anxiety),
- Pain and disability,
- Stroke, and even
- Premature death.

In addition, people with sleep problems often have a **disrupted circadian rhythm**, the body's internal clock. Misalignment of this sleep/wake cycle disrupts and impairs many psychological and physiological functions, which may increase the risk of metabolic disorders.^{4,5}

It's critical to get sufficient sleep *and* keep your circadian rhythm in tune.

What is Melatonin?

Melatonin is a hormone that regulates circadian rhythm and promotes healthy sleep patterns.¹

Studies have found that the pineal gland's secretion of **melatonin** decreases with age, which can make it more difficult to get quality sleep.^{6,7}

Use of computers, cell phones, tablets, and other devices exposes users to **blue light**, which also decreases melatonin levels.⁸

Melatonin has been shown to **improve** the onset, duration, and quality of sleep.⁹⁻¹¹

Many Americans today take melatonin before bedtime.¹²

A Sugar-Free Option

Melatonin capsules, tablets, or drops have become part of the nightly regimen for many aging adults.

Scientists have now developed a convenient way to supplement with **melatonin**—a great-tasting, easy-to-chew, vegetarian-friendly **gummy**.

Some people like chewing on something tasty before bedtime, and melatonin **gummies** have become enormously popular.



There are some problems with commercial gummies, however.

Take a look at any gummy label in the store. Many of these gummy supplements contain **high** amounts of **sugar** as the first ingredient.

Sugar inflicts a myriad of deleterious effects, including impeding restorative sleep.¹³

The new gummies are different. Each tasty gummy provides **3 mg** of melatonin and is **100% sugar-free**.

So, you can chew on the number of gummies that provide a low-calorie way of satisfying hunger while individually **dosing** the amount of **melatonin** that works best for you.

Many will find it a delicious way to get ready for bed.

Melatonin Promotes Healthy Sleep in Five Ways

In **human** studies, scientists have demonstrated that **melatonin** improves **five** parameters of sleep.

Clinical studies suggest that taking oral melatonin:⁹⁻¹¹

- *Reduces* **sleep onset latency**, the time between lights out and falling asleep,
- *Increases* **sleep efficiency**, the percentage of time we spend asleep while in bed,
- *Increases* **total sleep time**, time spent asleep after sleep onset,
- *Reduces* **wakefulness after sleep onset**, time spent awake after sleep begins, and
- *Synchronizes* and maintains a healthy **circadian rhythm**, to promote healthy sleep patterns.

In one meta-analysis of **17** studies involving a total of 284 volunteers, researchers found that, on average, **melatonin** use significantly:⁹

- *Reduced* **sleep onset latency** by **4.0 minutes**,
- *Increased* **sleep efficiency** by **2.2%**, and
- *Increased* **total sleep time** by **12.8 minutes**.

Syncing Circadian Rhythm

Nearly *every* cell in our body has an internal “clock” which is governed by a “master clock” in the brain that responds to changes in light exposure and helps create and maintain our **circadian rhythm**.¹⁴

Among other functions, circadian rhythm regulates our **sleep-wake cycle**. The body **increases** melatonin levels as light levels fall in the evening and **lowers** melatonin levels as light levels rise around daybreak.¹⁴

If circadian rhythm becomes *disrupted*, as may happen with age, this cycle can become impaired.

A study from the prestigious journal *Lancet Psychiatry* revealed that disrupted circadian rhythms are associated not only with sleep disturbances, but also with an increased risk of **depression** and **bipolar disorder**.¹⁵

Endogenous **melatonin** plays a critical role in keeping this central clock in sync with the environment, maintaining our circadian rhythm and improving sleep.^{16,17}

Oral melatonin has also been used to help **synchronize** the circadian rhythm in **blind** individuals whose bodies have been unable to synchronize with the day-night cycle.¹⁸

Help for Insomnia Sufferers

Insomnia is defined as difficulty initiating or maintaining refreshing sleep. It can have a drastic effect on daily life and health.

Low melatonin levels have been linked to insomnia, particularly in the elderly. Clinical studies have reported **serum** melatonin levels to be significantly **lower** (and the time of peak melatonin values delayed) in elderly subjects with insomnia compared with age-matched normal controls.¹⁹

A meta-analysis of 14 randomized controlled trials, of which insomnia was the primary diagnosis in 12 studies, found that people with insomnia who took melatonin had reduced **sleep onset latency** (the time it takes to fall asleep).²⁰

Another review found that oral melatonin provided a significant improvement in both **sleep onset latency** and **total sleep time** in those suffering from insomnia.²¹



WHAT
YOU
NEED
TO
KNOW

Get a Better Night's Sleep

- An age-related decline in **melatonin** levels can interfere with falling and staying asleep.
- **Inadequate sleep** is associated with the risk of obesity, type II diabetes, stroke, premature death, and more.
- Taking oral melatonin at night helps people **fall asleep faster** and **stay asleep longer**.
- Melatonin can also improve quality of sleep for patients with **insomnia** and help relieve symptoms of **jet lag**.
- Melatonin is now available in a great-tasting vegetarian **gummy** that is *sugar-free*.



Relief for Jet Lag

The energy-sapping effects of **jet lag** are a symptom of disrupted **circadian rhythm**.²²

Your body doesn't recognize the change when you fly into new time zones. As a result, the body's rhythms are suddenly out of step with the day-night cycle at your destination.

Oral **melatonin** can help to get your circadian rhythm back on schedule.

One review found that oral melatonin, taken close to the target bedtime at the destination (10 pm to midnight), was **remarkably effective** in preventing or reducing jet lag.²³

Similarly, melatonin may help shift workers adjust their sleep timing after a shift rotation.²⁴

These and other benefits make melatonin a safe, effective way to relieve sleep problems and promote optimal sleep.

Summary

Difficulty falling asleep and staying asleep can be caused by an age-related decline in levels of **melatonin**.^{6,7}

Not getting enough **sleep** is associated with a higher risk of obesity, diabetes, cognitive decline, stroke, shortened telomeres, and premature death.^{2,3}

Taking oral melatonin at night has been shown to improve **five** different aspects of sleep, helping to support overall health.⁹⁻¹¹

Scientists have developed a vegetarian, **sugar-free gummy**—a delicious *new way* to boost nighttime melatonin levels. ●

If you have any questions on the scientific content of this article, please call a **Life Extension Wellness Specialist** at 1-866-864-3027.

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



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



Caution: Temporary flushing, itching, rash, or gastric disturbances may occur.

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People often crave something tasty to chew on before **bedtime**.

A new strawberry-flavored **gummy** lets you dose your **melatonin** based on how many **gummies** you ingest before bedtime.

Clinical studies show that **melatonin** improves revitalizing **sleep** in five ways.¹⁻³

Each **sugar-free gummy** provides **3 mg of melatonin**.

For full product description and to order **Melatonin Gummy**, call 1-800-544-4440 or visit www.LifeExtension.com



1. *Sleep Med Rev.* 2005 Feb;9(1):41-50. 2. *Lancet.* 1995 Aug 26;346(8974):541-4. 3. *Neurol Res.* 2017 Jun;39(6):559-65.

Caution: Do not consume alcohol, drive or operate machinery after taking this product.

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VITAMIN K2'S Heart Health Benefits



BY ANTHONY PAYNE, N.M.D., PH.D., M.D. (HONORARY)

Vitamin K2 is best known for helping to build strong, healthy bones.

Some of the same skeletal benefits make it a powerful protector of the **cardiovascular system**.¹

Cardiovascular disease is the leading killer in the U.S.² **Vitamin K2** may help to:^{1,3}

- Reduce arterial stiffness,
- Slow the progression of arterial and valve calcification,
- Lower the incidence of diabetes, and
- Decrease cardiovascular mortality.

In one study, adults 55 and older were followed for up to **10 years**. Those with the *highest* intake of **vitamin K2**, compared to the *lowest*, had a **57%** lower risk of death from coronary heart disease—and a **26%** lower risk of death **from any cause**.⁴

About Vitamin K

There are two main types of **vitamin K**.⁵

Vitamin K1 is primarily found in green leafy vegetables. It has long been used to promote healthy **blood clotting** and prevent abnormal bleeding.⁵

Vitamin K2 is also known as **menaquinone**. It is essential for the health of bones and the cardiovascular system. Emerging evidence indicates it may play a vital role in **immune** function and in the health of the nervous system.¹

Vitamin K2 exists in several forms. Among these, **menaquinone-4 (MK-4)** and **menaquinone-7 (MK-7)** have been studied most extensively.^{6,7}

MK-4 is found mainly in dairy foods. **MK-7** is primarily found in fermented foods, such as kefir (fermented milk) and sauerkraut.^{5,8}

Preventing Atherosclerosis

In the U.S., over **650,000** people die from **heart disease** each year. That's roughly **one in every four deaths**.²

More than half of these deaths are from **coronary artery disease**, caused by a buildup of **plaque** (made of fats, calcium, and other substances) in the walls of arteries that restricts blood flow.²

This buildup is known as **atherosclerosis**. It can result in chest pain, **heart attacks**, and **strokes**.^{9,10}

Daily oral intake of **vitamin K2** may *prevent* atherosclerosis from progressing.

Last year, the **American Heart Association** released research showing that *higher* vitamin K intake was associated with significantly lower risk of **hospitalizations** resulting from atherosclerotic cardiovascular disease.¹¹



Combating Arterial Stiffness

One of the most significant ways **vitamin K2** protects against cardiovascular disease is by preventing **arterial stiffness**.

This physical stiffening of arteries contributes to cardiovascular disease.¹²

Vitamin K2 activates **matrix Gla**, a protein that helps prevent **calcium** from being incorporated into **arterial** tissue.¹

It also activates another protein that binds calcium to **bone**. This strengthens bone while at the same time helping to prevent **calcification** of our **arteries**.

Protecting Endothelial Function

All blood vessels are lined with a very thin layer of cells called the **endothelium**. This tissue helps regulate the flow of **calcium** and other substances into and out of the bloodstream.^{13,14}

A healthy endothelium is needed for optimal cardiovascular health.¹⁵

Endothelial dysfunction is a major contributor to aging, atherosclerosis, hypertension, and the complications of diabetes.¹⁵

It is characterized by an imbalance in the constriction and relaxation (dilation) of arteries, a decrease in nitric oxide bioavailability, and an increase in reactive oxygen species and pro-inflammatory factors.¹⁵

A hallmark of many types of cardiovascular disease is **endothelial dysfunction**.

When endothelial cells cannot function properly, plaque builds up and calcifies, and narrows the artery.¹⁶

Vitamin K provides cardiovascular protection thanks to its role in calcium homeostasis.

In a preclinical study, giving **vitamin K2** to mice prone to developing atherosclerosis increased nitric oxide production. This improved the ability of arteries to dilate.¹⁷

A **2021** review published in *Open Heart Journal* stated that:

*"Increased vitamin K2 intake may reduce arterial stiffness, slow progression of vascular and valvular calcification, lower the incidence of diabetes and coronary artery disease, and decrease cardiovascular mortality."*³

WHAT
YOU
NEED
TO
KNOW

Real-World Results

The heart-protective effects of **vitamin K2** have been demonstrated in multiple studies.

In observational studies, *higher* intakes of vitamin K2 were associated with *lower* rates of **arterial calcification** and **death** from coronary artery disease.¹⁸

In one study, women with the *highest* K2 intake were found to be at a **20% lower** risk for coronary artery **calcification** than women who had the lowest intake.¹⁹

Researchers analyzing more than 16,000 Dutch women who were followed for an average of 8.1 years found that *each 10 mcg/day increase* in vitamin K2 intake was associated with a **9% reduction** in coronary heart disease risk.²⁰

In another study, researchers followed more than 4,800 adults over age 55 for up to **10 years**.⁴

Overall, those with the *highest* K2 intake had a **57% lower** rate of death due to **coronary heart disease** and a **26% lower** rate of **death from any cause**.⁴

Safety of High-Dose Vitamin K2

Research suggests that **higher doses** of vitamin K2 intake are most likely to prevent the development or progression of cardiovascular disease.

In clinical studies involving daily K2 doses ranging from **10 mcg to 135 mg**, there have been **no reports** of adverse side effects.²¹ (The vitamin K2 dose of **135 mg** is very high by historic standards, yet no toxicity was observed.)

Protecting the Heart with Vitamin K2

- Cardiovascular disease is the leading cause of death in the U.S. It is frequently driven by **atherosclerosis**, buildup of plaque in arteries.
- **Vitamin K2** can help prevent and reduce calcification in arteries. It also reduces endothelial dysfunction, further decreasing atherosclerosis risk.
- In observational studies, those with the *highest* intake of vitamin K2 have *lower* rates of heart disease and as much as a **57% lower** rate of death due to **coronary heart disease**.

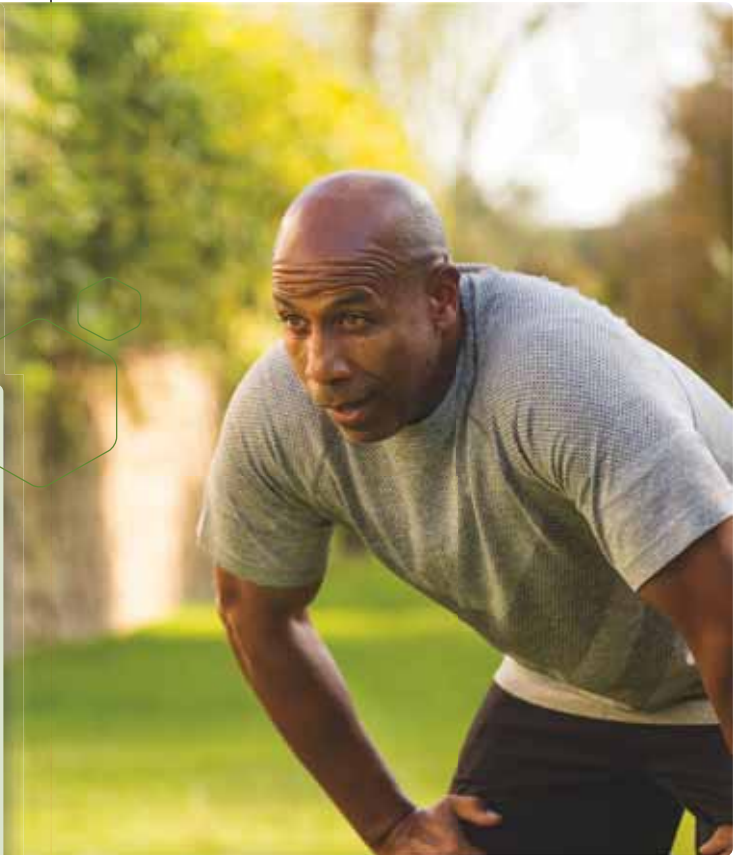
Japanese doctors routinely prescribe **45 mg** of vitamin K2 daily to women with **osteoporosis**.^{21,22}

These amounts may also help prevent the progression of atherosclerosis.

Summary

Vitamin K2 helps prevent arterial stiffening, buildup of plaque in artery walls, and endothelial dysfunction.

These and other actions reduce the development and progression of **atherosclerosis**, a major cause of heart disease. ●



A Warning About Warfarin

Anyone taking the anticoagulant drug **warfarin** should consult a physician before taking any form of vitamin K.

That's because *warfarin* *interferes* with the action of vitamin K in the body. Those taking newer anticoagulant drugs such as **Eliquis®**, **Pradaxa®**, and **Xarelto®** do not need to restrict vitamin K intake.

If you have any questions on the scientific content of this article, please call a **Life Extension** Wellness Specialist at 1-866-864-3027.

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Maintain Better Memory Function

VINPOCETINE

A compound originally found in the leaf of the periwinkle plant, vinpocetine has been shown to support brain health and memory function as people age.

Among its many benefits, vinpocetine has been shown to:

- Provide support for age-related cognitive decline
- Support healthy blood flow inside the brain



Item #01327 • 100 vegetarian tablets

1 bottle **\$13.50**

4 bottles \$10.50 each



For full product description and to order **Vinpocetine**, call 1-800-544-4440 or visit www.LifeExtension.com



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ZINC

UP

YOUR IMMUNE HEALTH

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Tina

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

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

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

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FOR HEALTHY BONES + HEALTHY HEART



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 – Dolores
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MEGA VITAMIN K2

Japanese physicians use **high-dose vitamin K2** for maintaining healthy bone density.



Vitamin K2 (MK-4) 45,000 mcg
 (for bone & vascular health)

SUPER K ELITE

Provides 2 additional forms of vitamin K and even **higher** potencies of K1, MK4, and MK7.



1
DAILY

Vitamin K1 2,000 mcg
 (converts to K2 in some people)

Vitamin K2 (MK-4) 1,500 mcg (for bone & vascular health)
Vitamin K2 (MK-7) 181 mcg (long-acting protection)
Vitamin K2 (MK-9) 43 mcg (added cardiovascular support)
Vitamin K2 (MK-6) 11 mcg (added cardiovascular support)

SUPER K

The best-selling **vitamin K** formula for bone and heart health.



1
DAILY

Vitamin K1 1,500 mcg
 (converts to K2 in some people)
Vitamin K2 (MK-4) 1,000 mcg
 (for bone & vascular health)
Vitamin K2 (MK-7) 100 mcg
 (long-acting protection)

Mega Vitamin K2 Item #02417 • 30 capsules
 1 bottle \$28.50 • 4 bottles \$26 each

Super K Elite Item #02335 • 30 softgels
 1 bottle \$18 • 4 bottles \$16 each

Super K Item #02334 • 90 softgels
 1 bottle \$22.50 • 4 bottles \$20.25 each

For full product description and to order these **VITAMIN K** formulas call **1-800-544-4440** or visit www.LifeExtension.com

CAUTION: If you are taking a vitamin K antagonist (e.g. warfarin), consult your healthcare practitioner before taking this product.



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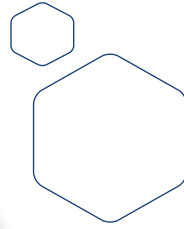
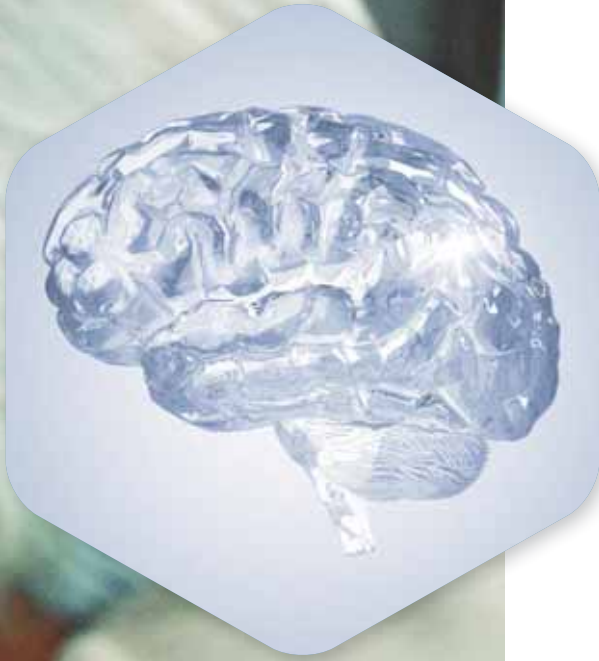
Systemic Benefits of N-ACETYL-L-CYSTEINE

BY LAURIE MATHENA

NAC (N-acetyl-L-cysteine) helps to replenish **glutathione** levels in the body.¹

Glutathione fights the **oxidative stress** that is closely associated with many *age-related* chronic disorders.²

But **NAC** does much more than this.



Applications for NAC

NAC is used in the medical setting as an antidote against **acetaminophen** poisoning.

Research interest has grown steadily over the years for its potential use in various pulmonary, cardiovascular, neurodegenerative, and liver disorders.¹

It protects against a broad array of **environmental toxins** and helps boost the body's **immune** system.¹

NAC supports healthy **respiratory tract** function and may be of value when combating bronchitis and chronic obstructive pulmonary disease.¹

The benefits of NAC extend to:¹

- Non-alcoholic steatohepatitis,
- Arterial hypertension of diabetic etiology,
- Chronic obstructive pulmonary disease (COPD),
- Chronic bronchitis,
- Male infertility,
- Cataract,
- Dry eye syndrome,
- Diabetic retinopathy, and
- Age-related macular degeneration.

NAC's Brain Benefits

Researchers summarized preclinical evidence showing NAC's ability to ameliorate symptoms and pathologies related to various psychiatric disorders.

They concluded that NAC is a strong candidate as an adjunctive approach for many psychiatric disorders.³

The progression of neuronal deterioration in certain areas of the brain may contribute to the development of **depressive** disorders.

In a rat model of depression, researchers found that NAC exerted antidepressant effects by helping protect neurons from injury. They concluded that NAC could be a potent therapeutic strategy for stress-related **depression**.⁴

Evidence continues to emerge for the benefits of this safe, inexpensive intervention.

Suggested Dosage

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

If you have any questions on the scientific content of this article, please call a **Life Extension** Wellness Specialist at 1-866-864-3027.

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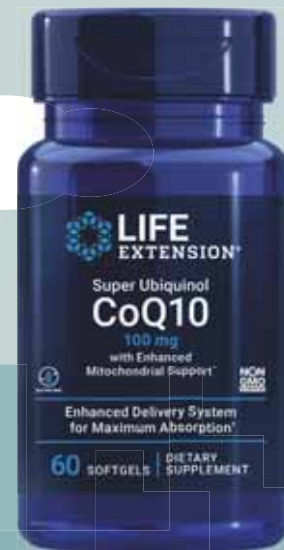
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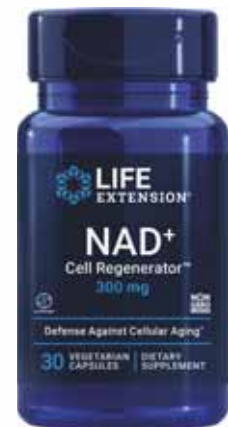
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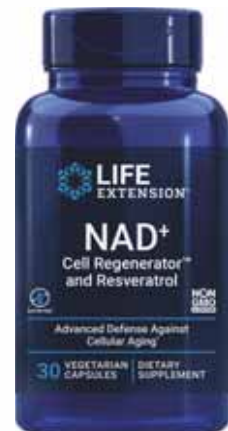
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Multiple Benefits of **NAD⁺**

- Energy production
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- Immune cell signalling



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It's given me tons of energy."

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For those already taking resveratrol, **NAD⁺ Cell Regenerator™** provides **300 mg** of **nicotinamide riboside chloride**.

Optimized NAD⁺ Cell Regenerator™ combines **300 mg** of **nicotinamide riboside chloride** with **resveratrol** and other **plant extracts**.

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* For pricing available to readers of this magazine, call **1-800-544-4440** or visit **LifeExtension.com/NAD**

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"NAC is a powerful tool."

Maury

VERIFIED CUSTOMER REVIEW

TAP THE POWER OF N-ACETYL-L-CYSTEINE TO SUPPORT IMMUNE FUNCTION

N-Acetyl-L-Cysteine (NAC) has been shown to support healthy immune response and respiratory function.

NAC supports healthy levels of *glutathione* that helps promote a healthy **inflammatory response** and protect cells from **oxidative damage**.

For full product description and to order **N-ACETYL-L-CYSTEINE**, call **1-800-544-4440** or visit www.LifeExtension.com

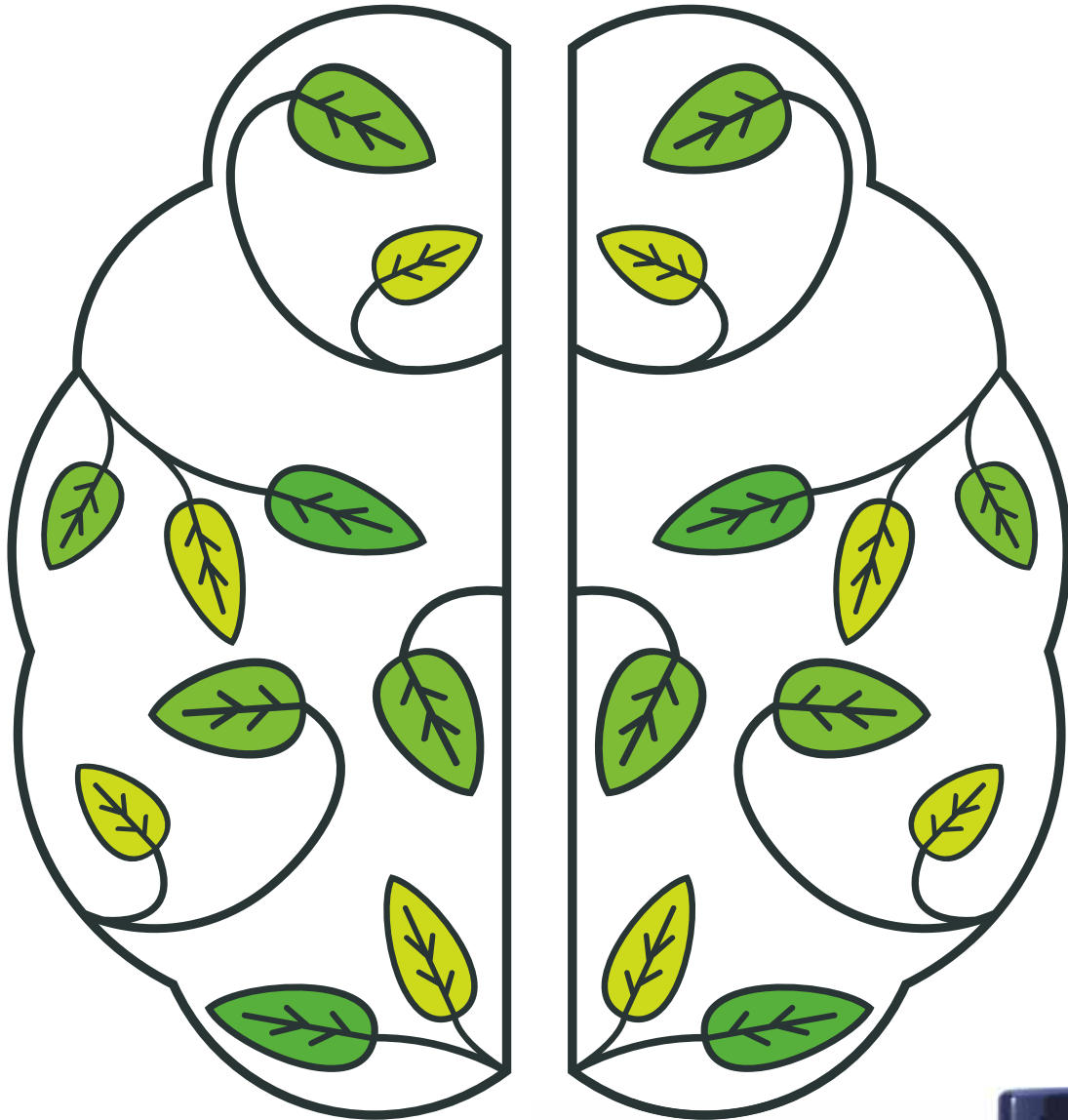


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Optimized Ashwagandha EXTRACT

Ashwagandha has been shown to:

- Support a healthy response to everyday stress
- Promote emotional well-being
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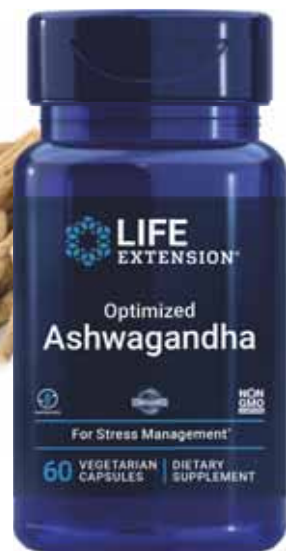
Optimized Ashwagandha provides **standardized** leaf and root **extracts** at a low cost.



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1 bottle \$7.50 • 4 bottles \$6.75 eac

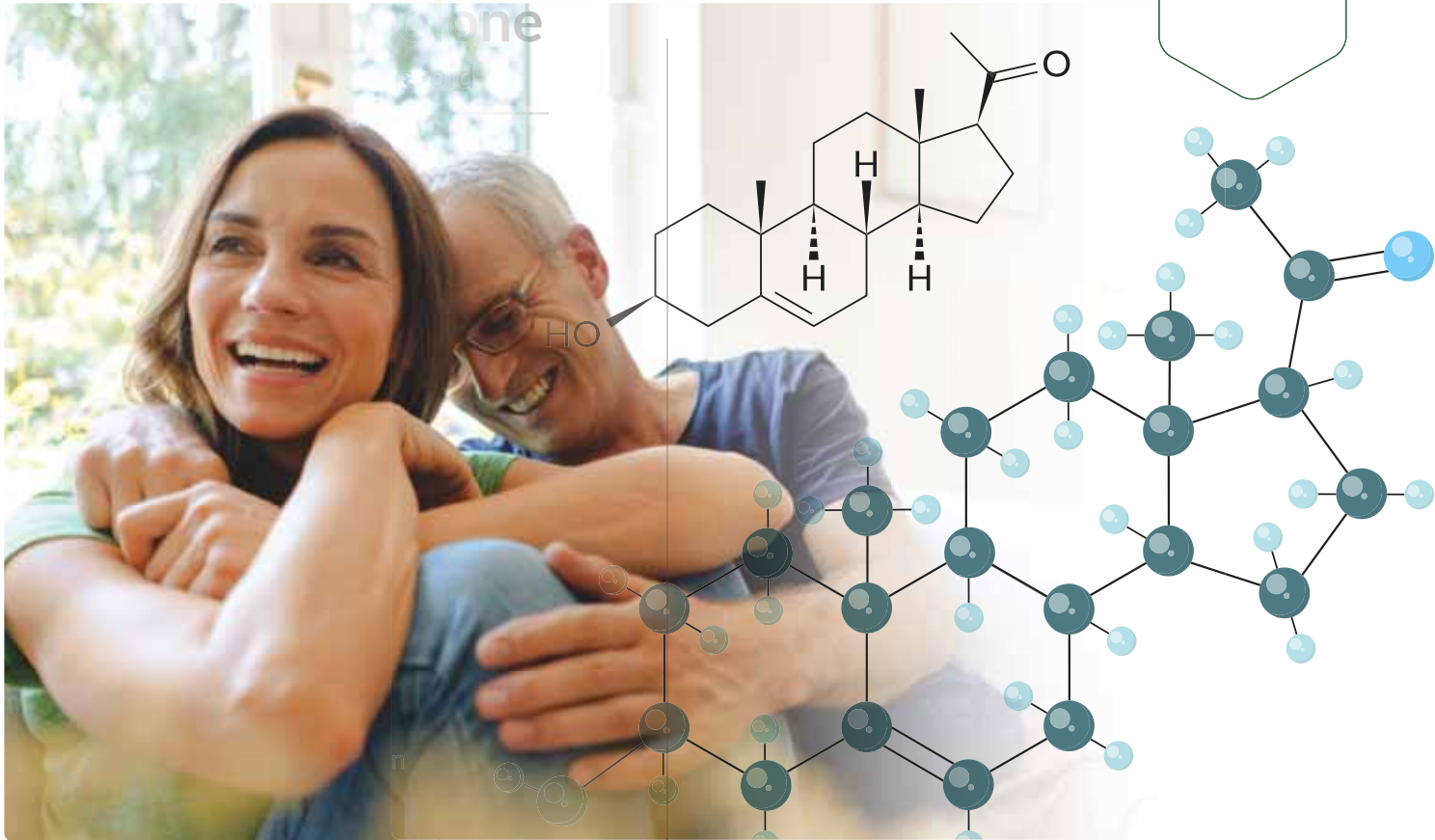
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For full product description and to order **Optimized Ashwagandha**, call **1-800-544-4440** or visit www.LifeExtension.com

What Is Pregnenolone?

BY LAURIE MATHENA



Pregnenolone is a hormone naturally produced in the body.

It has beneficial properties of its own and converts to other hormones such as **DHEA**, **progesterone**, **estrogen**, **testosterone**, and **cortisol**.

For this reason, it is sometimes called the mother of all hormones.

The body's production of pregnenolone declines with age as does that of DHEA, progesterone, estrogen, and testosterone.^{1,2}

Reduced Back Pain in Military Veterans

Previous studies have associated **pregnenolone** with improved memory, increased cognition, and elevated mood.³⁻⁵

A recent study highlighted another benefit: It significantly **reduced low-back pain** in Iraq- and Afghanistan-era U.S. military veterans.⁶

Compared to the **placebo** group, the **pregnenolone** group reported significant reductions in **low-back pain** at the end of the study.

They also reported **improvements** on scores for the degree to which their **pain** interfered with work and activity.

Based on the results of this study, the researchers suggest that **pregnenolone** could represent a novel, safe, and potentially effective treatment for **chronic low-back pain** in this population.

Improved Depression Symptoms

Low pregnenolone levels have been linked to **depression**.

In **clinically depressed** patients not receiving medication, researchers observed *lower* cerebrospinal pregnenolone levels, compared to healthy volunteers.⁷

In a clinical study, patients with **bipolar depression** were randomized to receive **pregnenolone** or a **placebo** as an add-on medication. After 12 weeks, researchers observed *higher* remission rates in the pregnenolone group than in the placebo group. The authors concluded that:

“The results suggest that pregnenolone may improve depressive symptoms in patients with bipolar disorder and can be safely administered.”⁸

Several **clinical trials** are now on the way.

At the **University of Texas Southwestern Medical Center** a clinical trial will evaluate the impact of **pregnenolone** on improvements in the severity of **depressive symptoms** in women.⁹

We look forward to reporting on human studies as their results are published.

Suggested Dosage

For those looking to support youthful hormone levels along with mental focus, memory, and more, optimal blood (serum) pregnenolone levels should be between **125-175 ng/dL**.

This can usually be achieved with daily pregnenolone doses ranging between **50 mg** and **100 mg**, preferably taken early in the day. •

If you have any questions on the scientific content of this article, please call a **Life Extension** Wellness Specialist at 1-866-864-3027.

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Pamela

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Systemic support for immune function, bone health, and normal blood-sugar levels.

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CAUTION: Individuals consuming more than 50 mcg (2000 IU)/day of vitamin D (from diet and supplements) should periodically obtain a serum 25-hydroxy vitamin D measurement. Do not exceed 10000 IU per day unless recommended by your doctor. Vitamin D supplementation is not recommended for individuals with high blood calcium levels.



Item #01713 • 5,000 IU • 60 softgels
1 bottle \$7.50 • 4 bottles \$6.50 each

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CUSTOMIZE YOUR **BONE-HEALTH** PROGRAM

Bone Restore helps maintain healthy bone density with three different forms of **calcium** plus vitamin D3 and magnesium, boron, zinc, manganese, and silicon.

Bone Restore with Vitamin K2, same formula as Bone Restore plus **200 mcg** of **vitamin K2**.

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Bone Restore

Item #01726 • 120 capsules

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Bone Restore with Vitamin K2*

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1 bottle **\$18** • 4 bottles \$16.50 each



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Item #02416 • 120 capsules

1 bottle **\$34.50** • 4 bottles \$31.50 each

For full product description and to order all **BONE RESTORE** products,
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* **CAUTION:** If you are taking a vitamin K antagonist (e.g. warfarin), consult your healthcare practitioner before taking this product.

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For Cognitive and Hormone Support



Pregnenolone provides systemic benefits, especially in the **brain**.

Beneficial mechanisms include modulating **brain plasticity** and promoting **neuronal health**.

Caution: Consult your healthcare provider before taking this product if you are at risk for or have been diagnosed with prostate or breast cancer. Do not take this product if you have a history of seizures.

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4. *Steroids.* 2016;111:54-9.
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Studies show that pregnenolone helps maintain:¹⁻⁵

- Memory
- Cognitive function
- Positive mood
- Mental focus
- Youthful sex-hormone levels

One daily capsule contains **100 mg** of pregnenolone.

Item #00700 • 100 capsules

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"I feel like things are much clearer and memory seems to be better."

Sharon

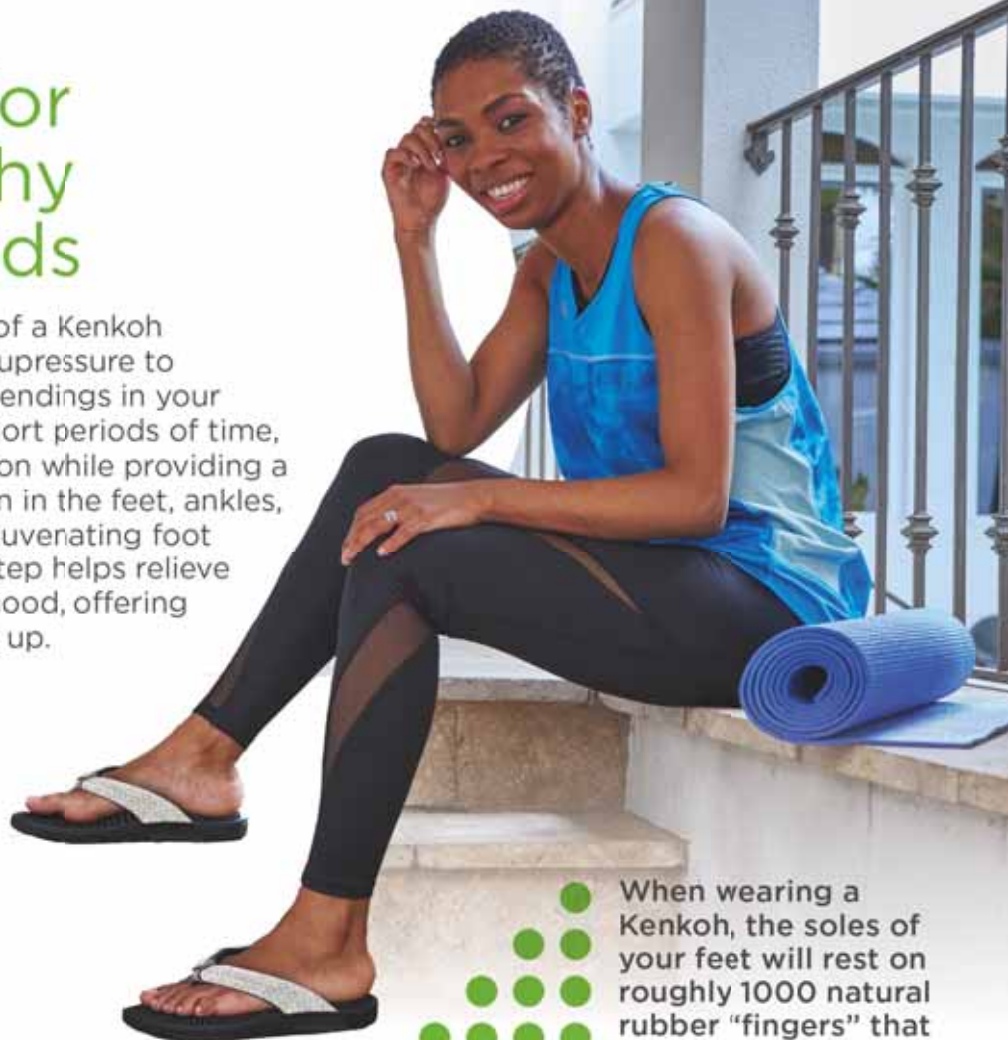
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For full product description and to order **PREGNENOLONE**, call **1-800-544-4440** or visit **www.LifeExtension.com**

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When wearing a Kenkoh, the soles of your feet will rest on roughly 1000 natural rubber "fingers" that will massage and stimulate key reflex points. This targeted therapy, known as reflexology, has long been practiced in Eastern cultures as a way of reducing pain, stress and anxiety.

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Dr. Gary Richter Discusses Whole-Food Nutrition for Our Pets

GARY RICHTER, DVM



Eating a whole-food diet is critical for a human’s optimal health and longevity, but what you feed your **pets** is important for their health and well-being as well.

Dogs get cancer at approximately the same rate as humans. They also suffer from heart disease, arthritis, allergies, gastrointestinal problems, and many other health issues that are similar to those faced by humans.

Their diet could be the reason.

As veterinarian Gary Richter explains here, standard dry and canned foods are highly processed foods that produce inflammation and harmful advanced-glycation end products in pets the same way that processed food does in humans.

Pet owners who switch to more natural diets for their animals report that the pets experience benefits like more energy, a healthier hair coat, better digestion, and dramatic improvements in gastrointestinal issues and allergies.

In this eye-opening interview with *Life Extension*®, Dr. Richter explains why standard kibble and canned food are so harmful for your pet. He also details the best foods to feed your pets to support their overall health.

—LAURIE MATHENA

LE: We know that eating a healthy diet is critical for humans, but how critical is it for our pets to eat an optimal diet as well?

Dr. Richter: Readers of *Life Extension*® are no strangers to the concept of optimal nutrition being a cornerstone of good health and longevity.

Even to the uninitiated, it is common knowledge that fresh, whole foods are better for your health than highly processed foods.

Despite it being self-evident when it comes to our own health and longevity, it is likely many have not considered the concept of fresh, whole food for our pets.

Every animal on earth evolved eating a fresh, whole-food diet, and that is how all biological systems evolved to function optimally.

After all, there were no bags or cans of food millions of years ago when evolution was hard at work developing what has become today's animal kingdom.

All species function at their best when they consume the nutrients on which their bodies are designed to thrive.

While an optimal diet clearly varies from one species to the next (herbivores, carnivores, omnivores, etc.), the common through line is that fresh, whole foods are best for all animals.

LE: Does this mean that standard canned and dry kibble isn't good for our pets?

Dr. Richter: With the understanding that an optimal diet for any animal is going to be made from fresh, whole foods, let's consider most pet food today.

Walk into any large pet store and you are faced with shelves full of kibble and canned food.

The companies that make these foods would have you believe these are "optimal" nutrition for your dog or cat.

They put pictures of fresh food on the labels and aggressively advertise on TV, in print, and on the Internet to let you know the food in that bag or can will keep your pet healthy and happy for a lifetime.

On closer examination however, the veneers of these foods peel back surprisingly easily.

LE: How can you distinguish a beneficial product from a harmful one?

Dr. Richter: Start by reading the ingredient list. Many middle-to-lower tier foods use meat by-products and meat meal as protein sources.

While some ingredients that go into by-products or meal could be healthy for your pet, we have no way of knowing what is actually in there. Some of the possibilities include hooves, horn, beaks, feathers, and wool.

Similarly, many pet food companies use carbohydrates like grains, legumes, etc., as a cheaper source of calories than meat and as a filler and binder for dry foods.

Dogs, and especially cats, are not evolutionarily adapted to high-carbohydrate diets.

LE: Is this a problem with premium brands as well?

Dr. Richter: Even the "premium" brands of pet foods are highly problematic for dogs and cats.

Read the ingredients of top-tier dry and canned foods and you will find ingredients that look good. In fact, they *are* good ingredients—or at least they *were*.

When you open that bag or can of food for your pet, how much does what you see resemble the high-quality fresh ingredients you read listed on the label?

LE: How have such inferior products become the standard diet for our pets?

Dr. Richter: A good thing to remember is dry and canned pet food exists for only one reason—our convenience.

The ability to have food for our pets that requires no refrigeration and is shelf stable for years is undeniably attractive.

The trouble is, preventing fresh food from spoiling without refrigeration often requires things to be done to the food that aren't necessarily in the best interest of our pets.

The shelf stability we see in most processed pet foods is achieved through the use of very high heat and pressure during processing. This kills pathogens that could lead to spoilage but creates a host of concerns that could prove harmful to our pets.

LE: Why is something like high heat problematic?

Dr. Richter: High heat and pressure frequently lead to loss of vital nutrients.

Anyone who has experienced overcooked meat or vegetables will instantly understand what this does to food.

You don't need to be a clinical nutritionist to recognize that overcooked food is not as nutritious as fresh or lightly cooked food.

As problematic as what is *missing* from highly processed pet foods is what is *created* during the high-heat and high-pressure cooking process.

Advanced glycation end products (AGEs) and Maillard reaction products (MRPs) are both produced as a result of proteins and carbohydrates being exposed to heat and pressure.

These chemical compounds are well known to promote inflammation and have been linked to cancer.

AGEs and MRPs are one of the main reasons why it is so important for people to eat fresh whole foods. It is also why fried foods and charred meats are frowned upon by nutritionists and longevity experts.

These foods cause inflammation in our bodies, and inflammation is the root cause of many chronic diseases experienced by humans and animals alike.

Perhaps one of the most disturbing aspects of processed pet foods is the amount of these toxins our pets are consuming.

When researchers evaluated the presence of MRPs in dogs and cats that consumed kibble or canned diets, it was found that dogs and cats consume 122 and 38 times more MRPs per day, respectively, than the average adult human!

LE: Are there any guidelines or regulations for what can and cannot be included in commercial pet food?

Dr. Richter: While there are nutrition standards set forth by the American Association of Feed Control Officials (AAFCO), these are minimum standards that ensure animals will not suffer from illness due to nutrient deficiencies.

These standards are largely concerned with macronutrients like protein and fat, and vitamins like vitamin A, B, C, D, etc.

There is no accounting for where the nutrients come from, as well as many micronutrients.

AAFCO standards provide an excellent minimum standard for pet food, but there is a lot of daylight between “minimum” and “optimal” nutrition.

If you want your car to function perfectly, you need to put in the type of gas and oil with which it was designed to function optimally.

The same is true for any biological specimen. It can function with minimum standards, but if you want it to work as well as it can for as long as it can, we need to do much better.

LE: If kibble and canned diets for our pets are so problematic, are there alternatives?

Dr. Richter: Fortunately, yes. And they don't all require you to home cook food for your dog or cat.

There are many fresh, whole-food diets for dogs and cats available in pet stores and on the Internet.

They come in several formats, including fresh-frozen cooked, fresh-frozen raw, freeze-dried raw, and dehydrated foods.

LE: What does an ideal diet look like for our pets?

Dr. Richter: In a perfect world our pets would all be eating either raw or lightly cooked diets. These diets are about as close to our pet's evolutionary diet as we can get.

These diets come in a variety of proteins and can be either purchased or made at home.

Clearly, buying food that merely needs to be thawed and fed is more convenient, but it also is more costly.

Making fresh food at home is an excellent, and more cost-effective option for people who don't mind spending a little time in the kitchen.

The goal with making food at home is to make as much food as you have space for in the freezer. Some people with multiple pets or large dogs purchase a chest freezer for the garage and store the pre-portioned food in there and thaw it as necessary.

The one critical thing to remember when making pet food at home is you must use a recipe balanced by a nutritionist. You cannot create a balanced diet by putting meat and vegetables in a bowl.

Books are available with balanced recipes and nutritionists are also available for consultations.

LE: You mentioned freeze-dried foods. Are these a good option for someone who doesn't want to make homemade food?

Dr. Richter: Freeze-dried and dehydrated foods are an excellent option for many pet owners.

Freeze-drying is a process by which moisture is removed from cold, fresh food under a vacuum, while dehydrating uses heat to remove the moisture.

Either way, the result is food that is shelf stable, weighs very little, and is much better for pets than more highly processed foods.

The amount of processing with freeze-drying and dehydrating does not lead to the degree of nutrient loss or the creation of AGEs and MREs we see in kibble and canned diets.

Feeding these foods is about as easy as it gets. Just add water.

LE: What about cost?

Dr. Richter: Freeze-dried and dehydrated foods are often a little less costly than frozen foods, and they have the added benefit of being shelf stable.

This is a great option for people lacking extra freezer space.

It's also great if you tend to travel with your pet. You won't need to worry about traveling with frozen food if you are using a freeze-dried or dehydrated option.

LE: What are the benefits of feeding our pets this type of food?

Dr. Richter: In my experience as a veterinarian, most people who convert their pet to a fresh, whole-food diet report having an overall healthier pet, with more energy, a healthier haircoat, and better digestion.

I have seen countless pets with chronic gastrointestinal issues and allergies dramatically improve on nothing more than converting to a fresh, whole-food diet.

LE: How difficult is it to switch your pet to a whole-food diet?

Dr. Richter: Switching to a fresh diet is easy.

The goal is to make a gradual transition. This allows your pet's digestive tract to make the adjustment from processed foods to fresh foods.

In addition, for picky eaters (I'm looking at you, cat owners), a very slow transition is often the key to getting pets to accept a new food.

Begin by adding a very small amount of new food to their old food. Each day, add a little more new food and take away a little more old food.

Depending on whether your pet has a sensitive GI tract or if it's a picky eater, take anywhere from one to three weeks in the transition.

There is no hurry. Take longer if you need to.

LE: Once you find a food that works for your pet, should you stick with that one food exclusively?

Dr. Richter: When it comes to fresh-food diets, there is no absolute right or wrong, although there are some good guidelines to follow.

Variety is a good thing to provide a spectrum of nutrients and to prevent dietary sensitivities caused by prolonged exposure to one protein over a very long period of time.

Some pets can easily switch from one protein to another with no problem, while others are a little more sensitive.

For our pet friends with sensitive tummies, consider a gradual transition to a new protein every three to four months.

Feeding more than one format of food is fine, as long as your pet does OK with it.

In other words, if you want to feed some fresh and some freeze-dried, that is fine. Some people do this so

their pet is accustomed to freeze-dried for when they go out of town with it.

Additionally, if it is financially challenging to feed your pet exclusively a fresh, whole-food diet, feed them as much as you can, and for the rest use high-quality canned food or kibble.

Just as with us humans, eating some fresh food and some processed food is better than eating exclusively processed foods.

LE: What about table scraps? Should you feed your pet food from your plate?

Dr. Richter: That depends on what you are eating.

Pets don't do well with spicy or highly seasoned foods so those should be avoided. Also, avoid foods high in fat as they can cause GI upset, and never give them foods containing onions, grapes, raisins, or macadamia nuts, as these can be toxic.

With that said, if you want to put a little something from your plate in your dog or cat's bowl, go ahead—sharing is caring.

Just make sure it's only a little because we want them to be mostly eating a fully balanced, fresh whole-food diet to meet all their nutritional needs.

LE: How difficult is it for a pet owner to make the switch?

Dr. Richter: Feeding your pet a fresh, whole-food diet is easier than it has ever been.

Whether you choose fresh frozen, homemade, freeze-dried, or dehydrated foods, you are taking the single biggest step anyone can take to ensure a long and healthy life for an animal.

The greatest thing about pet nutrition is that we are completely in control of what they eat.

It is much easier to feed a pet an optimal fresh, whole-food diet than it is for us humans. Their willpower doesn't come into play.

It's no secret how critical optimal nutrition is for human health and longevity. It is all the same for our pets. •

If you have any questions on the scientific content of this article, please call a **Life Extension** Wellness Specialist at 1-866-864-3027.

Dr. Gary Richter specializes in holistic veterinary care. From 2002-2021, he was the owner and medical director of Montclair Veterinary Hospital in Oakland, California. He launched Holistic Veterinary Care in 2009, also in Oakland.

His animal hospitals have received more than 30 local and national awards, including Best Veterinary Hospital, Best Veterinarian, and Best Alternative Medicine Provider. He was named one of the top 10 veterinarians in the US in 2012, America's Favorite Veterinarian in 2015, and he received the Holistic Practitioner of the Year Award in 2019.

Dr. Richter also wrote an Amazon Best-Selling book, *The Ultimate Pet Health Guide*. For more information, visit www.mypetthrives.com.



Bok Choy

BY LAURIE MATHENA



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Chinese cabbage—more commonly known as bok choy—is a cruciferous vegetable that’s been eaten in China for more than 1,500 years.

It continues to be a common ingredient in many Asian soups and stir-fries, but it deserves a spot at the table here in the US as well.

Bok choy has been ranked the **sixth** most nutrient-dense food (based on the Aggregate Nutrient Density Index).

Like other cruciferous vegetables, bok choy comes loaded with nutrients that can help reduce cancer risk, fight inflammation, reduce heart disease risk, and more.

People who eat more cruciferous vegetables like bok choy have a lower risk of numerous types of cancer, including lung, prostate, and colon cancer.¹

Bok choy contains selenium, an important mineral that helps detoxify cancer-causing compounds from the body. It’s also been shown to decrease the growth rate of tumors in rats.²

Bok choy’s “superfood status” comes from the variety of disease-fighting nutrients packed into its green leaves and crunchy white stalk.

For example, it contains the flavonoid quercetin, which helps reduce inflammation in the body.³

Like all other cruciferous vegetables, bok choy is rich in compounds called glucosinolates, which provide protection from serious diseases like cancer and myocardial infarction.⁴

Bok choy can be prepared in a variety of ways. Enjoy it shredded and tossed in a salad, chopped and added to soups, or sauteed with other vegetables. •

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- 01953 Pomegranate Complete
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- 02024 Triple Action Blood Pressure AM/PM
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- 02123 Bone Restore Chewable Tablet
- 02416 Bone Restore Elite with Super Potent K2
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- 01725 Bone Strength Collagen Formula
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- 01506 Dr. Strum's Intensive Bone Formula
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- 01476 Strontium Caps

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- 01974 Acetyl-L-Carnitine Arginate
- 02419 B12 Elite
- 02510 Brain Fog Relief
- 01659 CDP Choline
- 02321 Cognitex® Basics
- 02396 Cognitex® Elite
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- 02413 Dopamine Advantage
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- 01658 Ginkgo Biloba Certified Extract™
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- 00020 Lecithin
- 02101 Memory Protect

- 00709 Migra-Eeze™
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- 01706 Extraordinary Enzymes
- 02100 Gastro-Ease™
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- 00972 D-Ribose Powder
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- 01900 Energy Renew
- 01544 Forskolin
- 01805 Ginseng Energy Boost
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- 01904 NAD+ Cell Regenerator™ • 100 mg, 30 veg capsules
- 02344 NAD+ Cell Regenerator™ 300 mg, 30 veg capsules
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- 01500 PQQ Caps • 10 mg, 30 vegetarian capsules
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- 02003 Triple Action Thyroid

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- 00893 Brite Eyes III
- 02323 Digital Eye Support
- 01514 Eye Pressure Support with Mirtogenol®
- 01992 MacuGuard® Ocular Support with Saffron
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- 01873 Standardized European Bilberry Extract
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- 02218 Mega GLA Sesame Lignans
- 01983 Super Omega-3 EPA/DHA Fish Oil, Sesame Lignans & Olive Extract • 60 softgels
- 01988 Super Omega-3 Plus EPA/DHA Fish Oil, Sesame Lignans, Olive Extract, Krill & Astaxanthin
- 01982 Super Omega-3 EPA/DHA Fish Oil, Sesame Lignans & Olive Extract • 120 softgels

- 01985 Super Omega-3 EPA/DHA Fish Oil, Sesame Lignans & Olive Extract • 60 enteric coated softgels
- 01984 Super Omega-3 EPA/DHA Fish Oil, Sesame Lignans & Olive Extract • 120 enteric coated softgels
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- 01812 Provinal® Purified Omega-7
- 01640 Vegetarian DHA

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- 02171 Rainforest Blend Whole Bean Coffee
- 00438 Stevia™ Organic Liquid Sweetener
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- 01949 Super-Absorbable CoQ10 Ubiquinone with *d*-Limonene • 50 mg, 60 softgels
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- 00882 DHEA • 50 mg, 60 capsules
- 00607 DHEA • 25 mg, 100 vegetarian dissolve in mouth tablets
- 01689 DHEA • 100 mg, 60 veg capsules
- 02368 Optimized Broccoli and Cruciferous Blend
- 00302 Pregnenolone • 50 mg, 100 capsules
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- 01468 Triple Action Cruciferous Vegetable Extract
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- 00316 Kyolic® Garlic Formula 102
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- 01681 Lactoferrin (Apolactoferrin) Caps
- 02426 Mushroom Immune with Beta Glucans
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- 01309 Optimized Quercetin
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- 00525 ProBoost Thymic Protein A
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- 02133 GEROPROTECT® Longevity A.I.™
- 02401 GEROPROTECT® Stem Cell
- 02211 Grapeseed Extract
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- 01940 Super MiraForte with Standardized Lignans
- 02500 Testosterone Elite
- 01909 Triple Strength ProstaPollen™
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- 02107 Extend-Release Magnesium
- 01677 Iron Protein Plus
- 02403 Lithium
- 01459 Magnesium Caps
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- 01504 Optimized Chromium with Crominex® 3+
- 02309 Potassium with Extend-Release Magnesium
- 01740 Sea-Iodine™
- 01879 Se-Methyl L-Selenocysteine
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- 02428 Plant-Based Multivitamin
- 02317 Two-Per-Day Capsules • 60 capsules
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- 02303 Discomfort Relief

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- 00320 Dr. Proctor's Shampoo
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- 02304 Youthful Collagen
- 02252 Youthful Legs

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PROBIOTICS

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- 02250 FLORASSIST® Mood Improve
- 02208 FLORASSIST® Immune & Nasal Defense
- 02120 FLORASSIST® Oral Hygiene
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- 01920 FLORASSIST® Throat Health
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- 00056 Jarro-Dophilus EPS® • 60 veg capsules
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- 80154 Advanced Lightening Cream
- 80155 Advanced Peptide Hand Therapy
- 80175 Advanced Probiotic-Fermented Eye Serum
- 80177 Advanced Retinol Serum
- 80152 Advanced Triple Peptide Serum
- 80140 Advanced Under Eye Serum with Stem Cells
- 80137 All-Purpose Soothing Relief Cream
- 80139 Amber Self MicroDermAbrasion
- 80118 Anti-Aging Mask
- 80151 Anti-Aging Rejuvenating Face Cream
- 80153 Anti-Aging Rejuvenating Scalp Serum
- 80179 Brightening Peptide Serum

- 80176 Collagen Boosting Peptide Cream
- 80156 Collagen Boosting Peptide Serum
- 02408 Collagen Peptides for Skin & Joints
- 80180 CoQ10 and Stem Cell Rejuvenation Cream
- 80169 Cucumber Hydra Peptide Eye Cream
- 02423 Daily Skin Defense
- 80141 DNA Support Cream
- 80163 Eye Lift Cream
- 80123 Face Rejuvenating Anti-Oxidant Cream
- 80109 Hyaluronic Facial Moisturizer
- 80110 Hyaluronic Oil-Free Facial Moisturizer
- 80138 Hydrating Anti-Oxidant Facial Mist
- 00661 Hydroderm
- 55495 Intensive Moisturizing Cream
- 80103 Lifting & Tightening Complex
- 80168 Melatonin Advanced Peptide Cream
- 80114 Mild Facial Cleanser
- 80172 Multi Stem Cell Hydration Cream
- 80159 Multi Stem Cell Skin Tightening Complex
- 80122 Neck Rejuvenating Anti-Oxidant Cream
- 80174 Purifying Facial Mask
- 80150 Renewing Eye Cream
- 80142 Resveratrol Anti-Oxidant Serum
- 01938 Shade Factor™
- 02129 Skin Care Collection Anti-Aging Serum
- 02130 Skin Care Collection Day Cream
- 02131 Skin Care Collection Night Cream
- 80166 Skin Firming Complex
- 02096 Skin Restoring Ceramides
- 80130 Skin Stem Cell Serum
- 80164 Skin Tone Equalizer
- 80143 Stem Cell Cream with Alpine Rose
- 80148 Tightening & Firming Neck Cream
- 80161 Triple-Action Vitamin C Cream
- 80162 Ultimate MicroDermabrasion
- 80173 Ultimate Peptide Serum
- 80178 Ultimate Telomere Cream
- 80160 Ultra Eyelash Booster
- 80101 Ultra Wrinkle Relaxer
- 80113 Under Eye Refining Serum
- 80104 Under Eye Rescue Cream
- 80171 Vitamin C Lip Rejuvenator
- 80129 Vitamin C Serum
- 80136 Vitamin D Lotion
- 80102 Vitamin K Cream

SLEEP

- 01512 Bioactive Milk Peptides
- 02300 Circadian Sleep
- 01551 Enhanced Sleep with Melatonin
- 01511 Enhanced Sleep without Melatonin
- 02234 Fast-Acting Liquid Melatonin
- 01669 Glycine
- 02308 Herbal Sleep PM
- 01722 L-Tryptophan
- 01668 Melatonin • 300 mcg, 100 veg capsules
- 01083 Melatonin • 500 mcg, 200 veg capsules
- 00329 Melatonin • 1 mg, 60 capsules
- 02503 Melatonin • 3 mg, 60 gummies
- 00330 Melatonin • 3 mg, 60 veg capsules
- 00331 Melatonin • 10 mg, 60 veg capsules
- 00332 Melatonin • 3 mg, 60 veg lozenges
- 02201 Melatonin IR/XR
- 01787 Melatonin 6 Hour Timed Release
300 mcg, 100 veg tablets
- 01788 Melatonin 6 Hour Timed Release
750 mcg, 60 veg tablets
- 01786 Melatonin 6 Hour Timed Release 3 mg, 60 veg tablets

- 01721 Optimized Tryptophan Plus
- 01444 Quiet Sleep
- 01445 Quiet Sleep Melatonin
- 02502 Rest & Renew

VITAMINS

- 01533 Ascorbyl Palmitate
- 00920 Benfotiamine with Thiamine
- 00664 Beta-Carotene
- 01945 BioActive Complete B-Complex
- 00102 Biotin
- 00084 Buffered Vitamin C Powder
- 02229 Fast-C® and Bio-Quercetin Phytosome
- 02075 Gamma E Mixed Tocopherol Enhanced with
Sesame Lignans
- 02070 Gamma E Mixed Tocopherol & Tocotrienols
- 01913 High Potency Optimized Folate
- 01674 Inositol Caps
- 02244 Liquid Vitamin D3 • 50 mcg (2000 IU)
- 02232 Liquid Vitamin D3 (Mint) • 50 mcg (2000 IU)
- 01936 Low-Dose Vitamin K2
- 00065 MK-7
- 00373 No Flush Niacin
- 01939 Optimized Folate (L-Methylfolate)
- 01217 Pyridoxal 5'-Phosphate Caps
- 01400 Super Absorbable Tocotrienols
- 02334 Super K
- 02335 Super K Elite
- 01863 Super Vitamin E
- 02422 Vegan Vitamin D3
- 02028 Vitamin B5 (Pantothenic Acid)
- 01535 Vitamin B6
- 00361 Vitamin B12 Methylcobalamin
- 01536 Vitamin B12 Methylcobalamin • 1 mg, 60 veg lozenges
- 01537 Vitamin B12 Methylcobalamin • 5 mg, 60 veg lozenges
- 02228 Vitamin C and Bio-Quercetin Phytosome • 60 veg tablets
- 02227 Vitamin C and Bio-Quercetin Phytosome • 250 veg tablets
- 01753 Vitamin D3 • 25 mcg (1000 IU), 90 softgels
- 01751 Vitamin D3 • 25 mcg (1000 IU), 250 softgels
- 01713 Vitamin D3 • 125 mcg (5000 IU), 60 softgels
- 01718 Vitamin D3 • 175 mcg (7000 IU), 60 softgels
- 01758 Vitamin D3 with Sea-Iodine™
- 02040 Vitamins D and K with Sea-Iodine™

WEIGHT MANAGEMENT & BODY COMPOSITION

- 02479 7-Keto® DHEA Metabolite • 100 mg, 60 veg capsules
- 01807 Advanced Appetite Suppress
- 02207 AMPK Metabolic Activator
- 02504 Body Trim and Appetite Control
- 02478 DHEA Complete
- 01738 Garcinia HCA
- 01908 Mediterranean Trim with Sinetrol™ -XPur
- 01432 Optimized Saffron
- 00818 Super CLA Blend with Sesame Lignans
- 02509 Waistline Control™

WOMEN'S HEALTH

- 01942 Breast Health Formula
- 01626 Enhanced Sex for Women 50+
- 01894 Estrogen for Women
- 01064 Femmenessence MacaPause®
- 02204 Menopause 731™
- 02319 Prenatal Advantage
- 01441 Progesta-Care®
- 01649 Super-Absorbable Soy Isoflavones
- 02507 Youthful Woman 40+ with B-Complex



"I feel much more mentally clear."

Judith

VERIFIED CUSTOMER REVIEW

NEURO-MAG[®] THE SMART MAGNESIUM

SUPPORTS IMPROVEMENT IN
OVERALL COGNITIVE ABILITY*



With age, **synapses** that connect our brain cells wither.

Formulated by MIT scientists, **Neuro-Mag Magnesium L-Threonate** has been shown to improve **synaptic density** and other structural components of the brain.



Item #01603 • 90 vegetarian capsules
1 bottle \$30.75 • 4 bottles \$27.50 each



Item #02032 • 93.35 grams of powder
1 jar \$28.50 • 4 jars \$26 each

For full product description and to order **Neuro-Mag[®] Magnesium L-Threonate** or **Neuro-Mag[®] Magnesium L-Threonate Powder**, call 1-800-544-4440 or visit www.LifeExtension.com

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

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

FORESIGHT FOR YOUR EYESIGHT

MacuGuard® Ocular Support provides:

- > **Lutein, trans-zeaxanthin, and meso-zeaxanthin** help maintain structural integrity of the **macula** and **retina**.¹⁻⁵
- > **Cyanidin-3-glucoside** assists with night vision.⁶⁻⁸
- > **Saffron** has been shown to help support **vision** as demonstrated by doctors' eye exams.¹
- > **Alpha-carotene** further helps support **macular density**.¹



For full product description and to order either of these **MacuGuard®** formulas, call 1-800-544-4440 or visit www.LifeExtension.com

References

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2. *Nutrients.* 2013 April;5(4):1169-85.
3. *Nutrition.* 2011 Sep;27(9):960-6.
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7. *Invest Ophthalmol Vis Sci.* 2010;51(12):6118-24.
8. *J Agric Food Chem.* 2003 Jun 4;51(12):3560-3.

MacuGuard® Ocular Support with Saffron + Astaxanthin
Item #01993 • 60 softgels

1 bottle **\$33** • 4 bottles \$30 each

MacuGuard® Ocular Support with Saffron

Item #01992 • 60 softgels

1 bottle **\$18.75** • 4 bottles \$17.50 each

(Each bottle lasts for **two months**.)

MacuGuard® Ocular Support is available with or without astaxanthin.

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