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The Crucial Role of NAD+ in Optimal Health

Analysis by Dr. Joseph Mercola ✓ Fact Checked

April 10, 2022

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Nichola Conlon, Ph.D., Discusses
THE CRUCIAL ROLE OF NAD+ IN OPTIMAL HEALTH
MERCOLA
1:18:50

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STORY AT-A-GLANCE

- NAD+ (nicotinamide adenine dinucleotide) is one of the most important biomolecules in your body. It's involved in the conversion of food to energy, maintaining DNA integrity and ensuring proper cell function. Together, these functions help protect against or delay aging and disease
- NAD also acts as fuel for longevity proteins called sirtuins
- NAD levels dramatically decline with age, contributing to aging and chronic disease states. NAD is also used up by DNA repair enzymes and enzymes involved in inflammation and immunity, such that chronic inflammation, or acute illness in old age, can rapidly result in depletion
- To restore NAD, you need to fix the root cause for NAD depletion, which primarily involves addressing the decline in the NAD salvage pathway. By increasing enzymes in that pathway, which decline with age, your body can recycle NAD like it did naturally when it was younger

In this interview, Nichola Conlon, Ph.D., a molecular biologist, antiaging specialist and founder of a nutraceutical company that produces an NAD+ boosting supplement.

NAD+ (nicotinamide adenine dinucleotide) is one of the most important biomolecules in your body. It's involved in the conversion of food to energy, maintaining DNA integrity and ensuring proper cell function. Together, these functions help protect against or delay aging and disease. As explained by Conlon:

> *"NAD is actually something I ended up working on in the drug development industry. I was fortunate enough to work for a company that was forward thinking. It actually started looking at developing molecules that would improve our health span, which is the proportion of the life that we live in good health.*
>
> *So, rather than just focusing on individual diseases, we were actually looking at underlying mechanisms of cellular aging and looking at slowing cellular aging to improve healthy lifespan.*
>
> *This is when I came across NAD, which is an incredibly important molecule in the body. Going back to molecular biology roots, NAD is important for two critical things in the body.*
>
> *The first is energy production. The process that takes the energy out of the food we eat and converts it into ATP, which is the form of energy currency that our cells can use to survive and do all the functions that they need to do, absolutely requires NAD.*
>
> *Without it, we simply wouldn't be alive because our bodies wouldn't be able to make any energy. It's estimated that if we didn't have any NAD in our body, we'd literally be dead in 30 seconds, which shows how critical it is to our cells.*
>
> *The second thing that it's really important for is cellular maintenance and repair. NAD almost acts as a sensor in the body. It enables the cell to react to changes in energetic stress, which is basically how much energy or lack of energy the cell has ... These are the two major things that NAD is known for, and because of these roles, it's absolutely fundamental to overall cellular health."*

As an example, if you were to exercise or fast, that uses up cellular energy. NAD will sense this raised energy demand and increase its levels. Elevated NAD is actually a signal that the cell is in a state of stress. In response, cellular maintenance and repair processes are switched on to preserve the cell and help it survive the stress.

Some History

NAD plays a large role in the Krebs citric acid cycle as it helps to pass the electrons along in the mitochondria in the electron transport chain to facilitate oxidative phosphorylation and generate cellular ATP. While discovered in 1905, well over a century ago, few scientists have paid much attention to it.

In the late 1990s, David Sinclair, Ph.D., while working in Leonard Guarente's lab at Massachusetts Institute of Technology (MIT), realized that NAD is the fuel for longevity proteins called sirtuins. That's when it started coming into prominence as an anti-aging agent.

> *"It was around 2014 that I started getting involved in the aging field,"* Conlon says. *"This was a time when a lot of scientists were talking about this idea that we could slow cellular aging ... [Today], there isn't a single scientist that works in the field of biogerontology — the study of aging — who doesn't say that you can slow biological."*

Testing NAD Levels Is Complicated

Oftentimes, before you start supplementing something, you'll want to find out what your level is. Unfortunately, that's extremely difficult to do with NAD. We do know that NAD levels decrease with age, which is one of the reasons why people want to boost their NAD back to youthful levels.

> *"In scientific laboratories, we use some fairly sophisticated techniques to measure NAD,"* Conlon says, *"But now there's been an emergence of companies saying, 'Send your blood and we'll measure it for you.' The reality is, unfortunately, that as good as that would be, it just doesn't work that way.*
>
> *If you think of what NAD does, NAD is described as a redox molecule. What that means is, that it is continually flipping states. It carries electrons in the electron transport chain and [is involved in] the mitochondrial reactions. This means that by its very nature, NAD is designed to flip between different states, so it's really, really unstable.*
>
> *Literally, as soon as NAD is taken out of the body, it starts to break down into its precursors. It starts to change form. Therefore, if you don't do something to stop those reactions very, very quickly, what you end up measuring is not a correct reflection of what is actually in the body and in the cell.*
>
> *When we measure NAD in the laboratory, we have to make sure that as soon as it is taken out of the person, it's put straight on ice to stop any reactions and then immediately prepped to take out the cells that we want to measure the NAD from. They're then cryogenically frozen to stop any changes or any reactions until we measure the NAD. You've got around a 30-minute window to get this done.*
>
> *After that, to work out how much NAD is in the sample, you can then use techniques such as mass spectrometry, which compares the amount of NAD in the sample to standards, which are known amounts of NAD.*
>
> *These are not simple techniques. They are quite advanced laboratory techniques. So, when companies that say they can provide this as a postal service, at the moment, I'm quite skeptical of what they are actually measuring."*

How NAD Is Made and Regenerated

Your net NAD level is the sum of what your body makes minus what it loses. If you can successfully limit the amount being lost, then you can maintain your NAD level. So, how is it made, and how is it lost? Conlon explains:[1]

> *"It's incredibly complex. It's not just a simple case of adding two things together to make more NAD and that's the end of it. Within the cell, there are five different precursors that NAD can be made out of. These are the raw materials that your body uses to manufacture NAD ...*
>
> *You've got the B vitamins and derivatives nicotinic acid (nicotinamide), niacin, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN). And also the amino acid tryptophan. Once these are inside the cell, they enter various different pathways which then assemble them into NAD.*
>
> *There are three main pathways. The most important pathway for NAD production is something called the NAD salvage pathway. This is because not only can it make NAD from these external raw materials that come into the cell, but it can also recycle NAD as it is broken down.*
>
> *A key thing that many people don't realize is that when NAD is being used up in all of these beneficial processes in the cell, such as in DNA repair and activating other cellular pathways like the sirtuins, it actually gets broken down into one of its precursors, nicotinamide.*
>
> *The cell is really clever because what it's evolved to have is this salvage pathway, a recycling pathway for this nicotinamide (niacinamide). Which means that when NAD is used up, it gets broken down in nicotinamide and this nicotinamide then just gets recycled straight back into fresh NAD again.*
>
> *This makes absolute sense, because why would the body want to rely on generating such a critical molecule using external precursors? It needs to use something endogenous, something that it's always going to have a ready supply of.*
>
> *This also means that as demand for NAD goes up, more NAD is broken down in to nicotinamide, so technically there's more raw material that can simply be recycled straight back into fresh NAD again. This has been demonstrated to be the most important pathway for NAD production in the body.*
>
> *So when we're young, we've got this abundant supply of NAD that's continually being recycled via the salvage pathway. Unfortunately, as we get older, NAD declines. There are two main reasons for this. Firstly, more NAD is used up.*
>
> *When more NAD is used up, this means more needs to be recycled to replenish NAD. But it's also been found that that salvage pathway also declines with age. So right at this point in your life when you've got an increased demand for NAD, you've also got a reduction in the body's ability to regenerate NAD via this recycling route.*
>
> *When you put those two things together, what you get is an exponential decline in NAD, which is exactly what we see in human tissues throughout life. We see about a 50% reduction in NAD levels in our tissues every 20 years, which is quite shocking considering how important it is to our lives."*

How NAD Is Depleted

The thing that depletes NAD the most is when it's acting as a cofactor for other enzymes, such as the sirtuins and DNA repair enzymes. In that role, NAD acts much like a fuel, so it gets used up, causing your level to decline. In its energy production role, it merely flips between states, so the overall amount doesn't really change. The two primary enzymes that consume NAD are:

- **Poly ADP ribose polymerases (PARPs), especially PARP1, a DNA repair enzyme —** With age, the amount of DNA damage increases, which has to be repaired. One of the key enzymes that repairs this damage is called PARP1. For that enzyme to work, it needs NAD as a fuel. It literally takes NAD and breaks it down to form its reaction in the DNA repair action.

  "What you see is that if you've got increased levels of DNA damage in your tissues, you get increased activity of this enzyme and you get NAD depletion," Conlon says. Studies suggest extensive DNA damage within a cell can within five minutes deplete the NAD level in that cell to about 5% to 10% of what it started out with.

  One common exposure that causes DNA damage is electromagnetic field exposures (EMFs) from cell phones and wireless technologies. Some studies have shown that every time PARP1 is activated for DNA repair, it consumes 150 NAD molecules.[1]
- **CD38 —** Another enzyme called CD38, found on the surface of many immune cells, also consumes about 100 molecules of NAD for every cycle of its reaction. CD38 is a cell signal enzyme involved in sending calcium signals throughout the cell to activate parts of your immune system.

  "CD38 is one of the biggest NAD consumer in the body because of the fact that it is so inefficient at using NAD," Conlon says. "It's been found that even if you can inhibit CD38 by just a very, very small amount, you can have a significant impact on NAD levels because it is so inefficient."

The Challenges of Exogenous NAD Supplementation

Unfortunately, boosting NAD is no easy feat either. Many use NR or NMN, but the bioavailability of these is quite poor. It's kind of like swallowing bioidentical hormones. It's the real deal when you swallow it, but your liver has a tendency to want to detoxify and typically conjugates or adds in methyl groups to facilitate excretion. So, they don't really have time to transfer into your blood.

> **“It's clearly now demonstrated that to restore NAD, you need to fix the root causes. You need to fix that salvage pathway. You need to increase the enzymes in that pathway that are actually declining with age so that your body can recycle NAD like it did naturally when it was younger. ~ Nichola Conlon, Ph.D.”**

Conlon and her team discovered another way of boosting NAD.

> *"When we started looking at NAD, the first thing we did was to look for evidence that you could use molecules or supplements to boost NAD. At the time, everyone was looking at enhancing NAD levels with nicotinamide riboside or nicotinamide mononucleotide. which are the precursors or the raw materials that the body uses to make NAD.*
>
> *But there was no evidence that the reason that NAD was declining was because the body had a lack of availability of these precursors. In fact, still to this day, there's no evidence that our bodies have a reduced capacity to absorb these or that there's a reduced amount circulating in the plasma for the cells to use.*
>
> *Over the last couple of years, more understanding of NAD decline has emerged. It's clearly now demonstrated that to restore NAD, you need to fix the root causes. You need to fix that salvage pathway. You need to increase the enzymes in that pathway that are actually declining with age so that your body can recycle NAD like it did naturally when it was younger.*
>
> *You also need to look at these processes that are wasting NAD. You need to look at inhibiting CD38 and stopping chronic low level inflammation that's wastefully using up NAD. You also need to look at reducing DNA damage and being more efficient in its repair so you don't have this constant chronic activation of DNA repair, which is also using up NAD."*

Conlon and her team decided to pursue a multi-target strategy. Rather than just putting more raw material into the cell, the aim is to fix the cell. In experiments, they've demonstrated that you can boost NAD levels in the cells without putting any precursor in. You can actually just use ingredients that inhibit CD38 and activate nicotinamide phosphoribosyltransferase (NAMPT). This will boost NAD without having to add more raw materials to the cell.

NAMPT Is a Rate Limiting Enzyme for NAD Production

NAMPT is really important because that's the bottleneck, the rate limiting enzyme for the production of NAD. Conlon explains:

> *"The reason the salvage pathway declines with age is because of this one key enzyme. NAMPT actually recycles niacinamide and converts it into NMN, which then gets converted back into NAD. The rate limiting step, the bottleneck in that process, is NAMPT. And lo and behold, that is the key enzyme that declines as we get older.*
>
> *Studies have demonstrated that you get a 50% decrease in this enzyme between the ages of 45 and 60. That's a significant decline considering how important this is for new NAD production. The decline in the levels of this enzyme again correlate with the decline in NAD that we experience.*
>
> *Many diseases and issues that are associated with NAD decline are found to be because of a reduction in this enzyme. So, it's absolutely critical to try and improve the activation and expression of this enzyme in the body to enhance NAD. It worked brilliantly to give us high NAD levels when we were younger, so why not restore it back to that?"*

How Much Does NAD Decline Over Time?

NAD starts declining from the day you're born. For every 20 years thereafter, you lose about 50%. So, by the time you're 20, your NAD level is half of what you had at birth. By age 40, it's halved again from what you had at age 20, and so on. "It's an exponential curve," Conlon says, "Looking in elderly people's tissues, they really don't have very much left." I believe this may be one of the many reasons why elderly people are so susceptible to COVID. Perhaps even a primary one.

Conlon cites research showing SARS-CoV-2 infection does cause massive NAD depletion by over activating the PARPs. While PARP1 is involved in DNA repair, some of the other PARPs are involved in inflammatory responses, and they too need NAD.

> *"The running theory is that if we're older or sicker we have lower levels of NAD to begin with, so when we get infected, we're already at a lower starting point. So in someone who's younger and healthy and has high NAD, when they get infected, they've already got quite a good level to begin with, so even when they get that depletion, they can get by because they had adequate supplies to begin with.*
>
> *The other really interesting thing is what the cell does in response to the virus to try and mitigate this. All of the genes that the cell regulates to try and protect itself are all to do with NAD salvage. The body actively tries to increase NAMPT to protect itself because it knows that's the best way to produce NAD and rectify the problem."*

NAD Restoration for Optimal Health

According to Conlon, preclinical animal studies have shown NAD restoration really does help reverse disease and improve health span. In humans, using NR supplementation, the benefits have been less stellar. So far, they've not been able to replicate the preclinical models. Conlon suspects this is because NR and other precursors simply don't address the root causes of NAD decline.

> *“NAMPT is an enzyme, and you can get antibodies which will selectively attach to it. To measure it, we use a Western blot, which basically measures the amount of NAMPT protein that is available in the cell and it shows as a dark band. Basically, the darker the band, the more expression.*
>
> *Alpa lipoic acid works by increasing the activation of another energy sensor in the body called AMPK. AMPK is a sensor of any energy stress. When there's an energy stress in the body, AMPK goes up and it basically activates NAMPT so that it can increase NAD levels in the cells,"* Conlon explains.

Best and Least Expensive Way to Improve Your NAD+ Levels

So deeply appreciate Dr. Conlon's insights and expertise on NAD+ precursors. Although I have read dozens if not hundreds of papers on NAD+ the entire subject is confusing and I now realize it is likely because of financial interests that the best precursor is not recommended more frequently. Dr. Conlon has concluded, and I thoroughly agree with her, that the best single NAD+ precursor is niacinamide, not niacin, NR or NMN.

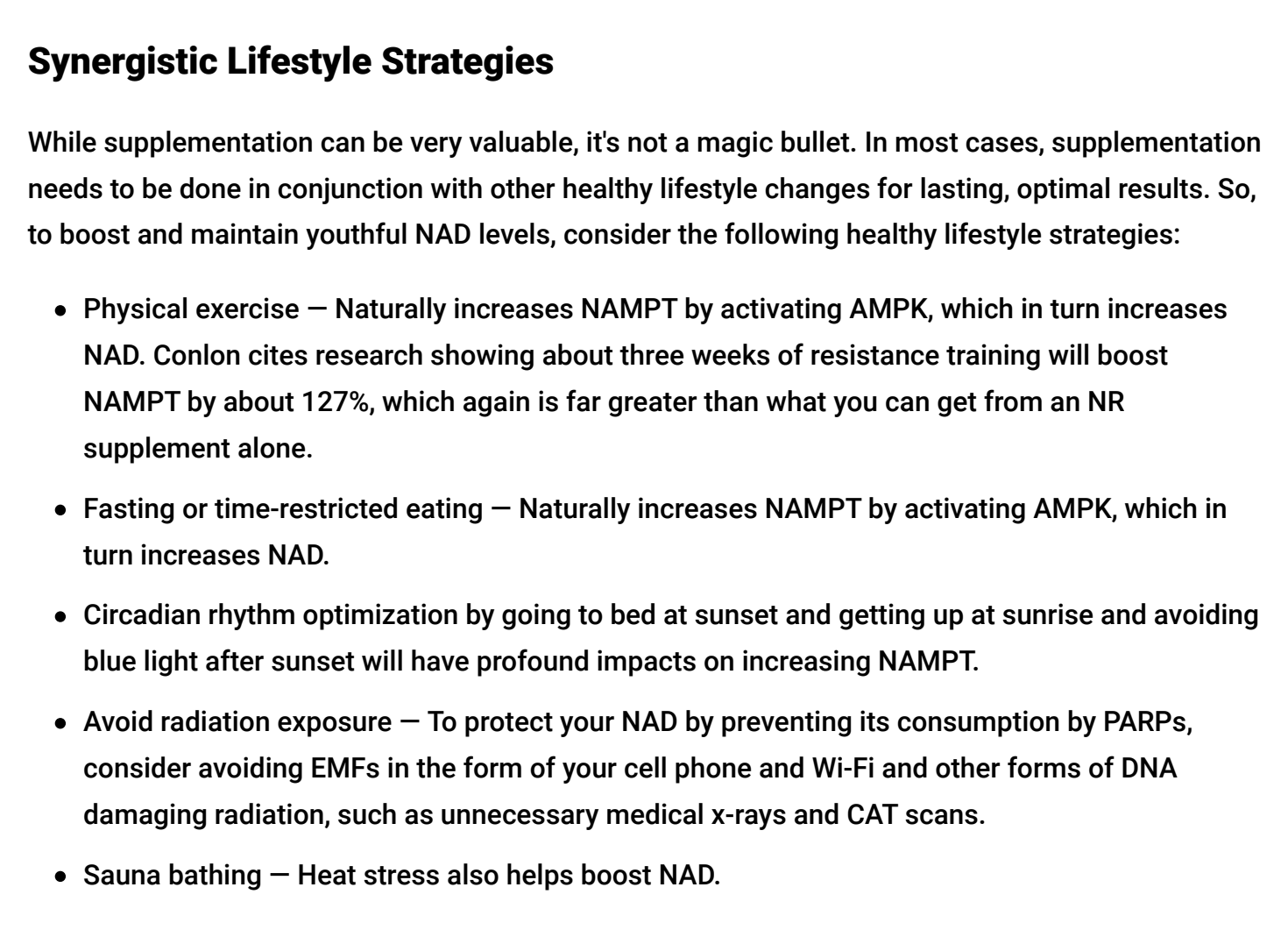
It is now beyond obvious to me why no one is promoting niacinamide. This is because it costs less than one cent a day and as a result there is simply no money to be made in promoting it. Ideally you buy niacinamide powder and use 1 to 1/2 of 1/64th of a teaspoon three times a day (25-50 mg).

You will need special measuring spoons to measure this small a dose. This is important as more is most definitely not better and much worse. If you use too much you will actually inhibit sirtuins which are important longevity proteins.

Spending $11 on 250 grams of niacinamide powder will give you a nearly four year supply of niacinamide. That pencils out to 23 cents a month or less than one penny a day. It is basically free. NMN in therapeutic doses of 1-2 grams/day can be one to two hundred dollars a month or 400-800X more expensive than niacinamide powder.

So let me review the reasons why Dr. Conlon and I both are convinced that niacinamide is the best NAD+ precursor. The immediate breakdown product of NAD+ is niacinamide and the enzyme NAMPT is the rate limiting enzyme in the salvage pathway to restore niacinamide back to NAD+. As you can see by the pathway below niacinamide is actually first converted to NMN before NAD+. This is likely why researchers like David Sinclair and others promote NMN.

However the enzyme NMNAT1-3 that converts NMN to NAD+ is not the rate limiting enzyme. Recall that NAMPT is what controls how much NAD+ you make. So you flooding your body with NMN is not going to be as useful as using small amounts of niacinamide and activating NAMPT as discussed below. Ideal dosing of niacinamide is from 25 to 50 mg three times a day. It is the rare person that will not respond favorable to this simple intervention for increasing NAD+.



NADH
NAD+
NADPH
NAD+ Breaks Down to Nicotinamide (NAM)
NMNAT1-3
NAM
NAMPT
NMN
NAD+ Rate Limiting Enzyme

Synergistic Lifestyle Strategies

While supplementation can be very valuable, it's not a magic bullet. In most cases, supplementation needs to be done in conjunction with other healthy lifestyle changes for lasting, optimal results. So, to boost and maintain youthful NAD levels, consider the following healthy lifestyle strategies:

- Physical exercise — Naturally increases NAMPT by activating AMPK, which in turn increases NAD. Conlon cites research showing about three weeks of resistance training will boost NAMPT by about 127%, which again is far greater than what you can get from an NR supplement alone.
- Fasting or time-restricted eating — Naturally increases NAMPT by activating AMPK, which in turn increases NAD.
- Circadian rhythm optimization by going to bed at sunset and getting up at sunrise and avoiding blue light after sunset will have profound impacts on increasing NAMPT.
- Avoid radiation exposure — To protect your NAD by preventing its consumption by PARPs, consider avoiding EMFs in the form of your cell phone and Wi-Fi and other forms of DNA damaging radiation, such as unnecessary medical x-rays and CAT scans.
- Sauna bathing — Heat stress also helps boost NAD.

Considering you can't really measure your NAD level, how can you your levels are improving? Conlon replies:

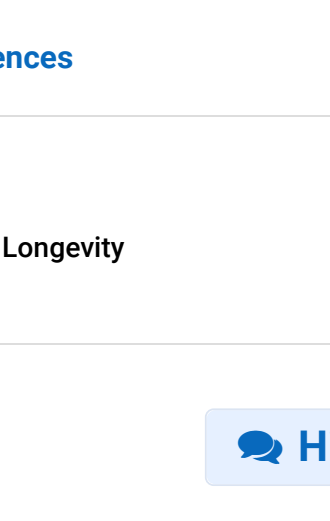
> *"We have three things that people always report back on. The first is energy levels, which is not surprising whatsoever given the key role that NAD has in the body of producing our energy. It's not an energy boost where people feel wired... It's more like having enthusiasm about the day — more 'get up and go.'*
>
> *The other thing is mental clarity and focus. And the final thing is sleep. NAD levels are actually circadian and cyclical and can fluctuate throughout your day ... As you get older and NAD levels decline, the peaks and troughs of NAD decline too which can hamper your circadian rhythm, which means your sleep quality isn't as good. Those are the three main things."*

I have a very optimized lifestyle that optimizes my NAD+ to youthful levels. I do this through an 18-hour daily fast in which I start my resistance training, and most days will follow that with an EMF-free sauna at 160 degrees F. for 20 minutes. I currently use 50 mg of the niacinamide powder I described above.

Even though I am rapidly approaching 70, my levels are that of someone much younger because of the activities I engage in that radically upregulate NAMPT. If you want to optimize your levels of NAD+, I encourage you to incorporate some of these strategies.

My #1 Bestselling Book – Now on Paperback!

My latest book, “The Truth About COVID-19,” is an instant bestseller. After thousands of reviews it has a nearly perfect 5-star rating, so grab your copy today before it's too late!



The Truth About COVID-19

by Doctor Joseph Mercola

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Guillermou
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Excellent report by Dr. Mercola on the transcendental importance of NAD in health and the routes to increase it. Nicotinamide adenine dinucleotide (NAD+) increases mitochondrial energy and its deficiency is an essential factor in chronic diseases and aging. NAD+ produces its beneficial effects in multiple pathological pathways, including mitochondrial dysfunction, DNA damage, and oxidative stress, by modulating enzymes such as sirtuins, glyceraldehyde-3-phosphate dehydrogenase, and AP endonuclease. www.liebertpub.com/.../ars.2017.7445 (2018) journals.lww.com/hnpjournal/Citation/2021/07000/Nicotinamide_Adenine_D.. (2021)

NAD is highly involved in various metabolic functions, such as glucose and fat regulation, and polymorphisms in these genes have been associated with the development of obesity, type 2 diabetes, cancer, cardiovascular disease. disease and longevity. Nutraceuticals such as resveratrol, quercetin, kaempferol, and curcumin and other therapies such as sirtuin activating compounds, NAD, nicotinamide mononucleotide) are being explored as potential therapies in sirtuin and point to promising treatments to promote metabolic health and reduce obesity and age-related diseases. journals.lww.com/jaanp/Abstract/2021/05000/Genomics_of_aging__The_role.. (2021)

NAD+ is a critical metabolic intermediate that serves as an enzyme cofactor in redox reactions, and is also used as a cosubstrate by many enzymes such as sirtuins, adenosine diphosphate ribose transferases, and synthases. Through these activities, NAD+ metabolism regulates a broad spectrum of cellular functions such as energy metabolism, DNA repair, regulation of the epigenetic landscape, and inflammation. NAD+ may have immunomodulatory properties on inflammation with a special focus on multiple sclerosis, inflammatory bowel diseases, and inflammation. bpspubs.onlinelibrary.wiley.com/.../bph.15477 (2021)

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NAD + improves learning and memory. Secondary endpoints also showed neuroprotective effects of NAD+ in different models of

Alzheimer's disease. Proposed neuroprotective mechanisms included, among others, attenuation of oxidative stress, inflammation, and apoptosis, while enhancing mitochondrial function. link.springer.com/.../s12031-021-01842-6 (2021) Aging is one of the main pathological factors associated with osteoarthritis. Sirt-1 may be involved in the pathology of degradation of articular cartilage in osteoarthritis, by a mechanism that binds the NAD-dependent deacetylase in Sirt-1 and its modulation by Runx2 in said pathology. www.oarsijournal.com/.../fulltext (2017)

Quercetin and apigenin increase NAD+ levels through inhibition of the multifunctional protein CD38 that is present in mitochondria, with a Sirt3-dependent mechanism. CD38 levels increase in tissues with age and correlate with decreased NAD www.timelesslifemag.com/index.php/2016/06/29/quercetin-apegenin-may-sl.. (2016) www.sciencedirect.com/.../S1550413116302248 (2016) Sirt-1-dependent NAD has an important role in human aging, the metabolic syndrome, chronic inflammation, and other diseases. Sirtuins, when the pattern of cellular metabolism is adjusted to the availability of nutrients, can regulate many metabolic functions related to aging: DNA repair, genome stability, inflammatory response, apoptosis, cell cycle, and mitochondrial functions. In regulating these functions, sirtuins cooperate with many transcription factors, including PGC-1a, NFkB, and p53. europepmc.org/.../26521204 (2016)

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This study reviews recent advances in the mechanistic understanding of biological aging, focusing on adenosine monophosphate-activated kinase (AMPK), sirtuin 1 (SIRT1), and mammalian target of rapamycin (mTOR) pathways, which are currently considered critical for ageing. We also discuss how these proteins and pathways can potentially interact with each other to regulate aging. www.mdpi.com/.../htm (2021) NAD+ depends on the family of 7 Sirtuins (SIRT1-7) that have a central role in NAD+ translation, changes in the regulation of many metabolic regulatory proteins, DNA repair, stress response, chromatin remodeling, circadian rhythm, and other cellular processes.

By mediating such broad functions, sirtuins are regulators for aging and longevity in various organisms. This article reports on associated diseases. NAD+ BIOSYNTHESIS, AGING, AND DISEASE f1000researchdata.s3.amazonaws.com/manuscripts/13118/9bc67958-db1a-44f.. (2018) NRPT is a combination of nicotinamide riboside and (NAD+), found in milk, and pterostilbene, a polyphenol found in blueberries, was administered to a population of 120 healthy adults between the ages of 60 and 80 years. The study consisted of three treatment groups: placebo, a recommended dose, and a double dose group. NAD + concentration increased by approximately 40% in the group and approximately 90% in the double administration group, after 4 weeks. www.nature.com/.../s41514-017-0016-9 (2017)

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juststeve
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Hey Gui, perhaps this is why babies & younger people are resistant, nearly immune to Covid?

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It is an important reference Just, aging and previous pathologies are the cause of serious Covid. NAD+ levels decline with age and oxidative stress over time. Also, during aging, decreased function of genes that control circadian rhythm can reduce NAD+ levels. In the mitochondria of the young, NADH can easily donate its electrons to generate NAD+. During the aging process, increased DNA damage reduces NAD+, causing mitochondrial dysfunction. www.ncbi.nlm.nih.gov/.../PMC4112140 (2014) .pubmed.ncbi.nlm.nih.gov/22848760 (2012) NAD+ activation of Sirtuins turns on genes that improve metabolism, aid in weight loss, and lower LDL cholesterol. Additionally, niacin and other NAD+ precursors are being tested as treatments for cardiovascular disease.

Nicotinamide riboside supplementation protected against diet-induced obesity. These animals may also burn fat better, burn more calories, and become more sensitive to insulin. Sirtuins improve glucose levels and glucose homeostasis www.ncbi.nlm.nih.gov/.../PMC3963134 (2014) www.ncbi.nlm.nih.gov/.../PMC4814520 (2016) SIRT1/NAD+ is important for the immune system to eliminate pathogens in part through the activation of MHC II. Hypoxia or low oxygen level prevents MHC II from being activated by decreasing SIRT1 activity (oxidized LDL also decreases SIRT1 in macrophages). academic.oup.com/.../2409095 (2011)

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As Dr. Mercola reports, CD38 is an enzyme found on the surface of many immune cells, it also consumes about 100 NAD molecules in each cycle of its reaction. CD38 is a cell signaling enzyme involved in sending calcium signals throughout the cell to activate parts of your immune system. The worldwide spread of the SARS-CoV-2 virus revealed specific susceptibilities to the virus among the elderly and those with age-related syndromes. These populations were more likely to experience a hyperimmune response characterized by refractory acute lung disease accompanied by multi-organ failure.

These observations underscore the interplay between the virus, the biology of aging, and the outcomes seen in the most severe cases of SARS-CoV-2 infection. Evidence to support the hypothesis that CD38 plays a central role in altered immunometabolism as a result of COVID-19 infection. The authors discuss a critical but underappreciated trifecta of CD38-mediated NAD, aging, and the COVID-19 immune response and speculate that the CD38/NAD 1 axis is a promising therapeutic target for this disease. europepmc.org/.../34494892 (2021)

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NAD acts as a cofactor in several oxidation-reduction (redox) reactions and is a substrate for several nonredox enzymes. NAD is critical to a variety of cellular processes, including energy metabolism, cell signaling, and epigenetics. NAD homeostasis appears to be of paramount importance for health and longevity, and its dysregulation is associated with multiple diseases. NAD metabolism is dynamic and is maintained by synthesis and degradation. CD38 dysregulation causes changes in NAD homeostasis and contributes to the pathophysiology of multiple conditions.

Indeed, in animal models, the development of infectious diseases, autoimmune disorders, fibrosis, metabolic diseases, and age-associated diseases, including cancer, heart disease, and neurodegeneration, are associated with altered CD38 enzyme activity. pubmed.ncbi.nlm.nih.gov/35138178 (2022) This study aimed to assess altered critical metabolic pathways with disease severity in hospitalized patients with COVID-19. The results show that obesity, respiratory rate, blood pressure and oxygen saturation, as well as some analytical parameters and radiological findings, were associated with the severity of the disease. Furthermore, ceramide metabolism, tryptophan degradation, and reductions in various metabolic reactions involving nicotinamide adenine nucleotide (NAD) at the time of inclusion were significantly associated with respiratory severity and correlated with inflammation. www.mdpi.com/.../htm (2021)

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juststeve
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Gui, I'm wondering if the NAD is different than the Niacin in B vitamin supplement? If so, would taking NAD along with the regular doses of Niacin or b-complex formula be an overload situation?

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Guillermou
Joined On 4/7/2015 8:47:48 AM
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Good thought, Just, I understand that individual metabolic processes to produce NAD may be different based on age, disease, and genetics. As Dr. Mercola reports, the "raw materials" or "building blocks" (metabolic precursors) that the body needs to make (synthesis) NAD+: 1.- Nicotinamide riboside (NR) 2.- Tryptophan (L-Trp) 3.- Nicotinic acid (NA; also commonly known as vitamin B3) 4.- Nicotinamide (NAM, also called "niacin without rinse") 5.- Nicotinamide mononucleotide (NMN) Supplementation with NAD+ precursors involved in "recovery pathways" (such as nicotinamide riboside and NMN) is relatively more effective at increasing cellular levels of NAD+ compared to those involved in the "de novo" pathway. This is because the NAMPT enzyme can act as a major limiting factor in NAD+ production. www.ncbi.nlm.nih.gov/.../PMC4112140 (2014) pubmed.ncbi.nlm.nih.gov/19286518 (2009)

Mark as Spam | Posted On 3/27/2022 5:53:42 AM

Like Dislike

Buddhii
Joined On 10/27/2020 2:36:40 PM
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Except that NAMPT inhibitors have potent anticancer activity in several preclinical models by depleting NAD+ and ATP levels. So there is that. Unfortunately. www.science.gov/.../nampt+inhibition+reduces And: "Elevated eNAMPT were reported in several metabolic and inflammatory disorders, including obesity, diabetes, and cancer, while eNAPRT is emerging as a biomarker of sepsis and septic shock." www.frontiersin.org/.../full The reasonable and intelligent question we have failed to ask is can one have too much NAD Plus. A possible speculative attempt at an answer, though not empirical, is we should not go past that which we had at age 20 or so.

Mark as Spam | Posted On 3/27/2022 9:32:35 AM

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Guillermou
Joined On 4/7/2015 8:47:48 AM
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Thank you Buddhi. The metabolism is very complex but the reality is that we must consider adopting natural measures for the prevention and cure of cancer. For example, fasting and exercise increase NAD and are a good treatment against cancer. In addition many phytochemicals enhance NAD and also the transcription factor Nrf2 which is essential for NAD production. academic.oup.com/.../4688715 (2004) Natural dietary phytochemicals, such as curcumin and resveratrol, are generally considered the most promising breast cancer preventive agents.

Nuclear erythroid factor-related factor 2 (Nrf2) is a transcription factor that plays a key regulatory role in the expression of multiple antioxidant and anti-inflammatory enzymes, which can effectively suppress excessive accumulation of carcinogens and their metabolites. The transcription factor Nrf2 is essential for the induction of NAD(P)H. Therefore, modulation of Nrf2 by dietary phytochemicals appears to be a promising approach for breast cancer prevention. pubs.rsc.org/en/content/articlelanding/2022/fo/d2fo00186a/unauth (2022) Very important is to consider the warburg effect, the propensity of some cells to metabolize glucose into lactate in the presence of oxygen has been observed for a long time in cancer and other contexts of cell proliferation, but only in the last two decades has it had significant gains . has been done to understand how and why this metabolic transformation occurs. aacrjournals.org/cancerres/article/81/19/4896/670303/Cancer-Signaling-... (2021)

Mark as Spam | Posted On 3/27/2022 10:23:21 AM

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Guillermou
Joined On 4/7/2015 8:47:48 AM
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NRF2 activation makes cells resistant to chemical carcinogens and inflammatory challenges. In addition to antioxidant responses, NRF2 is involved in many other cellular processes, including metabolism and inflammation, and its functions go beyond what was originally anticipated. NRF2 activity is tightly regulated through a complex transcriptional and post-translational network that allows it to orchestrate the cell's response and adaptation to various pathological stressors for the maintenance of homeostasis.

The complex regulatory network of NRF2 activity and its roles in metabolic reprogramming, unfolded protein response, proteostasis, autophagy, mitochondrial biogenesis, inflammation, and immunity. www.mdpi.com/.../4777 (2020) Nicotinamide (NAM) is a precursor to vitamin B 3 commonly sold over the counter as a nutritional supplement with anti-aging properties. Accumulating preclinical evidence indicates that NAM also mediates oncopreventive effects against a variety of neoplasms.

Supporting the translational relevance of dietary NAM supplementation, results from a Phase 3 randomized clinical trial demonstrated that oral NAM was safe and efficiently reduced the incidence of new non-melanoma skin cancers and actinic keratoses among individuals of high risk. However, the molecular and cellular mechanisms underlying this ability of NAM to delay carcinogenesis remain to be elucidated, as discussed in this short review. pubmed.ncbi.nlm.nih.gov/32383227 (2021)

Mark as Spam | Posted On 3/27/2022 10:23:52 AM

Like Dislike

Guillermou
Joined On 4/7/2015 8:47:48 AM
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NAD(H) and NADP(H) have traditionally been viewed as cofactors (or coenzymes) involved in a myriad of oxidation-reduction reactions, including electron transport in the mitochondria. However, NAD pathway metabolites have many other important functions, including roles in signaling pathways, post-translational modifications, epigenetic changes, and regulation of RNA stability and function through NAD protection of RNA. Nonoxidative reactions ultimately lead to net catabolism of these nucleotides, indicating that NAD metabolism is an extremely dynamic process. Indeed, recent studies have clearly shown that NAD has a half-life on the order of minutes in some tissues. www.sciencedirect.com/science/article/abs/pii/S1550413121001698 (2021) NAD+ precursor transporters and receptors are critical in maintaining cellular NAD+ levels. The tissue level of NAD + is maintained by the balance between NAD + biosynthesis and degradation. www.sciencedirect.com/science/article/abs/pii/S1550413121001698 (2021)

NAD precursors span pathways in cellular energy, inflammation, metabolism, and cell survival. Several metabolic and neurological diseases exhibit reduced tissue NAD levels, improved lifespan, and lifespan in animal models. Recent studies suggest a causal link between senescence, the age-associated reduction in tissue NAD, and the enzymatic degradation of the NAD precursor (nicotinic acid or niacin, nicotinamide, and nicotinamide riboside) that allowed a better understanding of its role in the cellular homeostasis, including signaling functions. that are independent of their + functions, information continues to evolve about the role of this molecule in health and disease. www.sciencedirect.com/science/article/abs/pii/S0026049521002237 (2022)

Mark as Spam | Posted On 3/27/2022 10:31:25 AM

Like Dislike

Guillermou
Joined On 4/7/2015 8:47:48 AM
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Extended-release niacin may have some muscle health benefits after chronic supplementation, as indicated by several molecular markers of mitochondrial biogenesis and muscle strength, although side effects related to flushing are of concern. Nicotinamide riboside supplementation was shown to increase muscle acetylcarnitine after exercise in one study; however, prolonged study duration and optimal dosing protocols may be necessary to show other benefits. Tryptophan has been shown to benefit exercise performance. faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.2021.35.S1.05282 (2021) Sirtuins are important regulators of energy metabolism; especially sirtuins 1 and 3 increase during exercise.

Sirtuin 1 has a positive effect on mitochondrial biogenesis, thus increasing mitochondrial energy supply capacity.+(which accumulates during exercise), as a substrate for sirtuins, is capable of upregulating the flow of sirtuins in a feedback manner . There is also an exercise-dependent upregulation of NAD+ synthesis. Sirtuin 4 regulates long-chain fatty acid oxidation by inhibiting malonyl CoA carboxylase. Elevated levels of malonyl CoA inhibit mitochondrial uptake of long-chain fatty acids. www.sciencedirect.com/.../B9780128141182000161 (2021)

Mark as Spam | Posted On 3/27/2022 10:32:26 AM

Like Dislike

Guillermou
Joined On 4/7/2015 8:47:48 AM
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Chronic age-related inflammation promotes cellular senescence, chronic disease, cancer, and reduced life expectancy. Interventional exercise, when applied early in the disease, was effective in reducing tissue inflammation, oxidative damage, and cellular senescence, and reversed hepatic steatosis and prevented tumor development. Behind these benefits were transcriptional changes in the enzymes that drive the conversion of tryptophan to NAD+. Increased SIRT activity correlated with increased deacetylation of the key transcriptional regulators of inflammation and metabolism, NF-κB. Moderate exercise can effectively reprogram inflammatory and metabolic pathologies pre-established in aging with the benefit of disease prevention. www.jimmunol.org/.../904.abstract (2021)

Mark as Spam | Posted On 3/27/2022 10:32:58 AM

Like Dislike

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marmur
Joined On 4/16/2008 1:07:05 AM
Add as Friend | Send Message

Dr. Mercola thank you for this article, interview and for every single thing you do to help humanity. You have put yourself in harms way with the evil people trying to control freedom. I support you by always buying my products from you. God bless you. Guillermou thank you for enhancing whatever subject Dr. Mercola brings to us. You are so wise and bring even more information that I savor. Thank you and Buddhi too!

Reply | Mark as Spam | Posted On 3/27/2022 11:22:03 AM

Like Dislike

Guillermou
Joined On 4/7/2015 8:47:48 AM
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Si, marmur, Dr. Mercola is a hero who defends humanity with true science with his health reports and the defense of freedom. . Thanks. for me it is an honor to be useful based on the excellent reports of Dr, Mercola.. ❤👍

Mark as Spam | Posted On 3/27/2022 12:11:46 PM

Like Dislike

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bradpais
Joined On 4/10/2017 1:11:23 PM
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Thanks Dr. Mercola for posting this. I've read about some of Dr. Sinclair's work in the past, sirtuins, NMN, methyl groups, C38, etc. It can be complicated. Perhaps my previous exposure to this field helped me absorb more of what you wrote here, which, by the way, really makes things more clear in ways other articles I read weren't able to do (for me, anyways). As usual, I love that you promote cheap alternatives, as I already have Niacinamide in my cupboard. All of this is a reminder that although our bodies are complex with all sorts of compensatory mechanisms that we are not aware of, good lifestyle choices (exercise, sleep hygiene, healthy foods high in methyl groups, limiting environmental hazards, etc) go a long way - in fact, way further than most of us are away of! PS: I forgot to note fasting! How could I forget to mention this (as Dr. M has)? So many benefits for so little a price (once you get used to it ;-)).

Reply | Mark as Spam | Posted On 3/21/2022 1:08:20 PM

Like Dislike

Guillermou
Joined On 4/7/2015 8:47:48 AM
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Yes, calorie restriction (CR) prolongs life expectancy in a wide variety of species. CR induces an increase in the NAD(+)/NADH ratio in cells and results in the activation of SIRT1, an NAD(+)-dependent protein deacetylase that is believed to be a metabolic master switch related to the modulation of exp of life. CR also affects the expression of peroxisome proliferator-activated receptors (PPARs). All three subtypes, PPARalpha, PPARgamma, and PPARbeta/delta, are expressed in multiple organs. They regulate different physiological functions such as energy metabolism, insulin action and inflammation, and apparently act as important regulators of longevity and aging. pubmed.ncbi.nlm.nih.gov/20148352 (2010) NF-kappa B is one of the main mediators of aging and is activated by toxic, oxidative, and inflammatory stresses.

The most abundant protein in the mitochondrial inner membrane, adenine nucleotide translocator 1 (ANT1) plays a critical role in mitochondrial function, including adenosine triphosphate/adenosine diphosphate (ATP/ADP) exchange in mitochondria, leakage of Basal proton and mitochondrial permeability transition pore (MPTP). ANT1 transcription is regulated by the transcription factor NF-kappa B (NF-kB). NF-KB signaling can repress ANT1 gene transcription and impair mitochondrial functions. Calorie restriction and fasting increase insulin sensitivity, Sirt1, and reduce inflammation. Insulin stimulates NF-kB impairing mitochondrial function. SIRT1 increases mitochondriogenesis, enhancing the oxidative stress response, p53-altered apoptosis, and decreasing the inflammatory response through NF-KB suppression www.nature.com/.../srep44708 (2017) www.ncbi.nlm.nih.gov/.../PMC3295063 (2018)

Mark as Spam | Posted On 3/27/2022 2:18:00 AM

Like Dislike

Guillermou
Joined On 4/7/2015 8:47:48 AM
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Sirtuins help cells adapt energy production. SIRT1 and some of the other sirtuins enhance fat metabolism and modulate mitochondrial respiration to optimize energy harvesting. The AMP kinase/SIRT1-PGC-1α-PPAR axis and mitochondrial sirtuins appear to be essential for maintaining mitochondrial function. Nutraceuticals like resveratrol have a multiplicity of actions in addition to sirtuin activation. Their net health benefit and relative safety may have stemmed from the animals' ability to survive environmental changes. www.sciencedirect.com/science/article/abs/pii/S089158491201756X (2013)

Mitochondrial sirtuins SIRT3, SIRT4, and SIRT5 function as the primary site of oxidative metabolism, control basic mitochondrial biology, and play crucial roles in energy production, apoptosis, and intracellular signaling. Its dependence on NAD + directly links its enzymatic activity to the metabolic state of the cell. In mammalian tissues, mitochondrial sirtuin expression and/or activity may decrease with age and contribute to mitochondrial dysfunction, an important hallmark of aging and the development of age-related diseases, including neurodegeneration, insulin resistance, and heart disease. www.sciencedirect.com/.../S1471491417300242 (2017)

Mark as Spam | Posted On 3/27/2022 2:18:16 AM

Like Dislike

Hel5896
Joined On 1/19/2021 7:57:37 AM
Add as Friend | Send Message

Wowsa! Dr. Mercola's never-ending search for human betterment combined with the desire to share what's learned with us is a gift. Many thanks, Doctor Mercola.

Reply | Mark as Spam | Posted On 3/27/2022 5:17:38 AM

Like Dislike

Prismmelody7
Joined On 7/24/2010 5:30:16 PM
Add as Friend | Send Message

I have had debilitating anxiety and panic from the virus. At first, I didn't realize it was from the virus. But after watching an FLCCC video on long haul, I realized it could be. I tried ivermtn and that helped tremendously. Since then, I have still been fighting inflammation, specifically, it seems like my heart has been overactive even though I was checked by a cardiologist and I appeared to be "fine." I read that Alpha Lipoic Acid could help with reducing inflammatory responses such as interluekin 6, so I tried it, and within hours it felt like a bucket of cold water was being poured on an electrical fire in my chest. I have been taking all kinds of anxiety supplement since I first had the panic attack that landed me in the ER: passionflower (a lot!), inositol, choline, PS100, melatonin, and something called True Hope.

They have all helped, but it has felt like I hadn't been addressing the underlying cause until the ivrmtn, then the Alpha Lipoic Acid. After reading this, I am going to try the Niacinamide. My energy gets depleted easily where I feel weak and feel I could have a panic attack. Yesterday was the first day in 4 months I was able to do a full weighted workout without feeling like I could have a panic attack, but overnight, it felt like my body was playing catch up. Panic is an awful feeling. I have had times when I felt like I was dying. I have a feeling it's somehow connected to what is described here. Thank you for this helpful article!!

Reply | Mark as Spam | Posted On 3/27/2022 10:00:03 AM

Like Dislike

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seedsaver37
Joined On 4/28/2020 2:58:31 AM
Add as Friend | Send Message

Prism, my sympathy goes out to you, that must be awful.. Having tried so many remedies, have you thought of trying homeopathy? People often turn to this when nothing else has worked, and I have heard first hand many encouraging stories, as well as having had personal success. Here is one link - as you can see, there is more than one remedy, as homeopathy treats the whole person, not just the symptom. homeopathyplus.com/anxiety-and-panic-attacks-tamed-by-homeopathy/

Mark as Spam | Posted On 4/10/2022 3:22:55 AM

Like Dislike

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junieb
Joined On 9/22/2009 9:22:04 PM
Add as Friend | Send Message

Wow, then we definitely don't want to be taking the 500mg capsules on sale! That is way too much!

Reply | Mark as Spam | Posted On 3/27/2022 2:41:14 AM

Like Dislike

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rrealrose
Joined On 11/10/2011 8:59:01 AM
Add as Friend | Send Message

take apart capsules (gently twist plastic sleeve) and store pwdr contents in a brown or blue liddled jar! Only issue then is excipients used to fill the caps in the first place...

Mark as Spam | Posted On 3/27/2022 8:57:26 AM

Like Dislike

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catspring47
Joined On 6/12/2013 11:09:32 AM
Add as Friend | Send Message

Junie The capsules will have fillers in them, so if you were to measure the contents to take the 1/64th tsp. dose, it would be very inaccurate. It might be worth it to pitch the capsules and get the pure powder.

Mark as Spam | Posted On 3/27/2022 9:38:59 AM

Like Dislike

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bee70578
Joined On 1/24/2014 4:03:10 PM
Add as Friend | Send Message

junieb - I've seen those, they seem to be diluted with other substances for most part, at least on UK Amazon. Good point.

Mark as Spam | Posted On 3/27/2022 10:34:58 AM

Like Dislike

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nancymat
Joined On 2/5/2015 9:32:29 AM
Add as Friend | Send Message

I noticed that each day's recommended serving of Dr. Mercola's Multi-Vitamin for Women has 40 mg of niacinamide and each day's recommended serving of his Vitamin-B Complex has 20 mg. I bought the niacinamide powder and a set of tiny spoons on Amazon last week and I've been using it three times a day. Because I have those other sources of niacinamide, I've been filling one-half of the tiniest spoon with the powder and popping it under my tongue. (I don't know why I picked that spot). I swear, I had incredible energy at work last week!

Reply | Mark as Spam | Posted On 4/10/2022 7:21:31 AM

Like Dislike

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lindatoo
Joined On 8/13/2016 8:34:22 PM
Add as Friend | Send Message

Blue berries in my yogurt will down the sups, nice thank you.

Reply | Mark as Spam | Posted On 3/28/2022 8:30:15 PM

Like Dislike

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junieb
Joined On 9/22/2009 9:22:04 PM
Add as Friend | Send Message

People can also do a search of "niacinamide powder" on Duck Duck Go, click on the link above the page that says "shopping", and it will bring up a list of products available from different retailers other than Amazon

Reply | Mark as Spam | Posted On 3/27/2022 10:55:15 PM

Like Dislike

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pjmauigirl
Joined On 4/14/2021 12:00:14 PM
Add as Friend | Send Message

Excellent information, thank you!

Reply | Mark as Spam | Posted On 3/27/2022 4:32:37 PM

Like Dislike

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brianjstiles
Joined On 6/19/2006 2:06:37 PM
Add as Friend | Send Message

One reader is complaining that Dr Mercola doesn't give details of where to order supplements mentioned in his newsletters specifically his one on NAD+....He does so in order to maintain impartiality.... I tried myself to obtain Niacinamide (aka Nicotinamide) powder in a pharmaceutical grade and it wasn't easy...Here is one source I found: www.amazon.co.uk/Pure-Vitamin-B3-Niacinamide-Powder/dp/B013KX00US?th=1

Reply | Mark as Spam | Posted On 3/27/2022 11:47:30 AM

Like Dislike

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seedsaver37
Joined On 4/28/2020 2:58:31 AM
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"Currently unavailable" Seems to hard to come by the powder, most is in capsules with 500mg.

Mark as Spam | Posted On 4/10/2022 3:11:04 AM

Like Dislike

jpw1
Joined On 6/19/2006 7:03:34 AM
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Peak Supplements in the UK sell it in powder form. Their smallest bag is 25g, which goes quite a long way and means you can try it out very cheaply. I bought metal micro-spoons on Amazon and am using 1 level 1/64th tsp three times a day. Too early to say about effects. I tried buying micro-scales (Peak Supplements recommend NOT using spoons, due to innaccuracy...), but the scales were not accurate, despite their spec suggesting they could measure 25 - 50mg. I sent them back and got a refund. I would have to spend too much to get micro-scales that would be capable of measuring that amount. The micro-spoon method is ok, but I'd much rather buy 50mg or 100mg capsules. Jon

Mark as Spam | Posted On 4/10/2022 5:51:11 AM

Like Dislike

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mindig
Joined On 2/27/2010 8:38:08 AM
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So I'm getting way too much niacinamide in my BComplex vitamin according to this information. I feel like I need to get a balance of the b vitamins and have not seen one that has these very small amounts of niacinamide. Not sure what to do........

Reply | Mark as Spam | Posted On 4/10/2022 7:20:44 AM

Like Dislike

WildDervish
Joined On 7/29/2020 9:08:38 AM
Add as Friend | Send Message

Question: I purchased Tru Niagen (nicotinamide ribocide chloride) and it makes me very energized in a not so good way, speedy. Is that common? What are some sirtuin supplements we can take? Thanks!

Reply | Mark as Spam | Posted On 4/10/2022 10:40:26 AM

Like Dislike

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jpw1
Joined On 6/19/2006 7:03:34 AM
Add as Friend | Send Message

Please can someone (Dr Mercola?) answer 2 questions. Why does he state the dose is 1 - 1/2 of 1/64th teaspoon, which is 25-50mg? Why is the teaspoon dose given largest first (1) followed by smallest (1/2), but the mg dose is the other way round? Normally you would say '1/2 to 1 (of 1/64th tsp) which is 25-50mg'. Is the 1 - 1/2 a misprint? Should it be 1 - 2? Secondly, I bought nicotinamde powder (from Peak Supplements in the UK) and they recommend consuming up to 100mg per day, which agrees well with Dr Mercola. But, most sellers (including Peak Supplements) also sell capsules with 500mg in them.

Why, if the maximum dose is around 100mg? A comment below said the capsules have a filler in them, which may be true, but they surely still contain 500mg of nicotinamide PLUS the filler? I questioned Peak Supplements on the difference between dose in powder and capsules and they could not answer except to say 'consumer choice'. I understand that capsules or powder is consumer choice, but maximum dose isn't - that is about safety. No-one sells 100mg capsules. Why?

Reply | Mark as Spam | Posted On 4/10/2022 5:03:04 AM

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