

## HOW POSTBIOTICS UPGRADE YOUR MITOCHONDRIA – DR. ANURAG SINGH – #877

Dave Asprey:

You're listening to the Human Upgrade with Dave Asprey, formerly known as Bulletproof Radio. Today is going to be a really fun interview because we're talking about something you probably haven't heard of even if you're a cool biohacker like me or like our Upgrade Collective live audience members. You've heard of probiotics because, hey, what the heck? I've been talking about those for a long time and so of many other people, and you can buy them even at a normal grocery store, healthy gut bacteria.

If you read Fastest Way or Superhuman, I talk a lot about prebiotics, the food for them, but you know what a postbiotic is? Probably not. Well, you will by the time we're done with the show today. We're going to dig in to studies on what happens after gut bacteria digests something and then look at what it makes and what that can do to renew your mitochondria.

Our expert today is Dr. Anurag Singh, who's an MD, PhD, and the Chief Medical Officer from a company called Amazentis SA. He's designed big clinical development and translational research, which means he looks at the science stuff and says, "How do we turn it into real world that you can actually use?" We're going to dig deep on mitophagy and how to turn that on. What the heck is mitophagy and why would you want to listen to something about that? Because replacing the dim bulbs or the dim batteries in your cells is important if you want to live a long time, you want to function at your best today, and you need to start that process even when you're young so that you don't get old, and if you're old, you want to turn that up so that you can get young. It's just harder to do once you've already accumulated a lifetime of, well, dim bulbs. You don't want to be one of those.

Dr. Singh, welcome to the show.

Dr. Anurag Singh:

Thanks for having me, Dave. Pleasure to be here.

Dave:

You're joining from Switzerland, where you spend most of your time. Thank you for staying up late for the Upgrade Collective, and for me to make this work. I want to know. I've looked at your career, and I mean, you've worked for big companies like Nestlé. You've authored 30 articles in science journals. You're a super science nerd. I don't know if in Switzerland that's an insult, but here, that's a compliment, but you've spent now seven years looking at just one compound called Urolithin A. I've covered it a little while back, maybe about a year or so ago. We talked about it briefly, but I want to dig deeper in it because the idea of postbiotics has intrigued me a lot. What got you into just one postbiotic for that period of time given that you've done a lot of cool stuff?

Dr. Anurag Singh:

Yeah. So you summarized my career well. I've spent the last 15 plus years running clinical trials in the nutrition and consumer health industry mostly on prebiotics and probiotics to start with big consumer health companies such as Nestlé Health. After that, what I realized was that it was not the symbiotic bacteria in your gut or what they needed to survive, which is the prebiotics, but what got me really interested was the end result of this bacterial metabolism, and that's this beautiful metabolite that was discovered at the Swiss Institute of Technology, of course, and then from there, commercialized by Amazentis, which is the company now I work for.

So seven years back, it was a lab discovery, and I'm trained as a doctor, a clinician, and then as a scientist in the US, and I often see scientists make a discovery and then say, "Okay. Let's move on to the next big one and forget about it." The doctors, well, they take a long time to realize what's happening in the science field. It's come to 10 plus years.

So I said, "Hey, this is something big. I can actually take this forward from the lab discovery scale to clinical science and to the breakfast table and daily life of people," and that's what we have done here for the last seven plus years. Yeah.

Dave:

So you got into this one because you're interested in mitophagy and you bounced around. I have to admire that. I have had the great pleasure to know a lot of what I'm going to affectionately call crazy inventors or crazy scientists, not tinfoil hat wearing crazy, but they're so into invention and creation that the idea that if you make something that no one ever uses or sees or they only see it in a journal article that got referenced 14 times so you feel good about yourself, it's like chasing likes on Instagram but for smart people, right?

Dr. Anurag Singh:

You got it.

Dave:

So you said, "All right. I'm going to actually do the hard work of getting people to do something that works instead of just to make stuff that works and then throw it over the edge of a cliff and then go make something else," which is one of my motivating things. I'll curate as much of those things as I can find and catch and then talk about. So I just want to offer my respect and congratulations for deciding that you're going to do that hard work of taking one thing and moving it actually to the goal, to the finish line instead of, like you're saying earlier, bounce around and do a bunch of stuff.

Dr. Anurag Singh:

Yeah. I mean, my mentor always said, "Research is basically two words, re and search," right? So you got to keep going back to the drawing table and asking the same question in different people, and different subjects, and different population. That's what we have done. Now, we're doing our fifth or sixth clinical study with this beautiful molecule. A lot of times in nutrition world, people put extracts and blends of probiotics together and they just give it to healthy people and expect magic to happen. Here, we've actually done the deep dive of the signs and the hitting how this molecule hits mitophagy and mitochondrial health, and then bringing it to human translation, I think, and to commercialization, as you said. This is really the holy grail for real world evidence.

Dave:

Can you walk me through mitophagy and what it is and then why you got into that out of all the fields you can look into?

Can you walk me through mitophagy and what it is and then why you got into that out of all the fields you can look into?

Dr. Anurag Singh:

Yeah. So mitophagy is basically recycling of the faulty mitochondria. So as we age, our cells accumulate faulty mitochondria. Now, in a life cycle of a mitochondria, what you have is basically you get new growth of mitochondria and this process is called mitochondrial biogenesis. As you age, these healthy mitochondria will accumulate free radicals and reactive oxygen species and they start to lose shape and they stop communicating well with each other much like think of it like battery. Now, if battery is not wired with each other, you're not really producing enough energy.

So this recycling process, as you put it, dim bulbs as you age, and that's what this molecule, Urolithin A, does is it revs up the recycling. So think of your recycling your trash can in your house. If you're accumulating waste in it but never cleaning it up, your house won't smell very nicely. That's what mitophagy is. You need to have mitophagy up and running as you age so that you're creating space for new healthy mitochondria to always produce energy, which is ATP.

Dave:

That idea of looking at it as recycling is really elegant. When you look at any of the antiaging things that are out there, and most of them anyway, there's some aspect of recycling there. You've doubtlessly seen probably Bruce Lipton is the one who talks about it the most, but lots of people reference a study where a researcher kept his whole culture life for a ridiculous amount of time by changing the medium all the time until his grad students got drunk and forgot to change the water, and lo and behold, the experiment ends.

It seems like that's happening inside each of the major components of our cells. It's happening extracellularly. So there's a lot of cleanup work to do if you want to stay young, and over time, you're going to accumulate metals, you're going to accumulate dysfunctional cells and all of that.

Are you feeling hopeful that we're going to be able to do enough cleaning of all the different systems including, obviously, mitophagy, but all the other stuff that we're going to be able to extend human lifespan that way?

Dr. Anurag Singh:

Well, I'm very optimistic that we'll be able to extend human health span, which is when you're 90 you're able to go about your activities of daily living. Now, how that translates into extended lifespan, this is something where active research is going on with what is the diet and certain blue zones where people live longer, but I am very optimistic that you can be a fit 90-year-old and play with your grandchild much.

Dave:

I don't know, Dr. Singh. I think that's a bit of a cop out. I'm going to share a little story here. Back when I was studying what we called computer information systems, it was one of the first degrees you could get in in what would now be called artificial intelligence.

I asked my professors, "Hey, why don't we just call this what it is?"

They said, "Oh, we can't call it artificial intelligence because no one believes artificial intelligence is real. It will never happen."

That wasn't that long ago, okay? That was certainly within my lifetime, right? It was only a decade or two. So when I hear that, "Oh, we're going to extend health span," it's like, "Oh, we shouldn't really say what we're doing because people might not believe us." Do you really think that a healthy 90-year-old who's playing with his or her grandkids isn't going to live longer as well?

Dr. Anurag Singh:

No. That's what I'm saying. First, you need to rev up the machinery to make the motor run well, and when the motor runs well, maybe the car will have a longer lifespan. So I'm just saying that I'm very optimistic that the data today says that health span can be extended. I think that ultimately may translate to extend the lifespan as you're saying.

Dave:

So you're hedging your bet so no one thinks you're crazy.

Dr. Anurag Singh:

No. I think given the knowledge we have today, we probably can realistically extend human lifespan, but what I'm saying is that as a focus as a clinician, a physician scientist, my first aspiration, I mean, there's many layers, right? You want to go to the moon before you want to go to Mars. So right now, we just want to aim to get to the moon and then I'm sure we'll get to Mars.

Dave:

I like that. So it's a goal. We'll probably get there and when and exactly how is open for interpretation. I hear you on that and I actually agree with you there. I'm just one to say within the next hundred years we'll get there. So that's good enough for me because I'm planning to be there.

Dr. Anurag Singh:

Okay. Great.

Dave:

How old do you think you're going to live?

Dr. Anurag Singh:

I think I want to beat my father and my grandfather in terms they both lived till 80 plus. So if I can as a third generation outlive them, I'll be happy then.

Dave:

Excellent. So you want to do better than the previous generation. I certainly expect my kids to outlive me. Hopefully, they can double my age if our tech keeps doing what it can do and we don't destroy the soil and the insect life on the planet because I'm pretty sure they're going to need it, but those are different issues that may affect longevity or maybe I'll live in bubbles on Mars. Just ask Elon. By the way, perchlorate, Elon, perchlorate. Different issue.

Now, when we eat something, we know that our gut bacteria will transform it, and when I say eat something, we're talking about pharmaceutical drugs. Many, many of the actions of pharmaceutical drugs are mediated by our gut bacteria, and we're figuring that out now. If you don't have the right gut bacteria, this drug doesn't work nearly as well or may not work at all. Yet, some drugs work regardless of your gut bacteria. It all depends.

Then we're getting all these natural compounds. I'm well-known for saying, "Hey, maybe you should have more polyphenols in your diet because they do all sorts of good stuff." Polyphenols are colored compounds, if you guys are listening and you're new to the Upgrade Collective or new to the

show. They're colored compounds that give red things their color and dark things their color like black rice or black coffee, tea, chocolate, et cetera, et cetera and, of course, pomegranates, which is where we're going to go deep today.

Pomegranates make something called ellagic acid. I'm one of the few people, actually, knows that I don't have gut bacteria that convert ellagic acid into the active compound that gives pomegranates most of their good benefits. There's two reasons pomegranates work. One is ellagic acid, the other one is PON1 enzyme, if it's fresh pomegranate juice, which is a detoxing enzyme that's probably not as important as the other thing.

So I used to have a pomegranate tree in my backyard. Didn't matter how much I ate. I could raise my blood sugar, but I couldn't raise my levels of beneficial mitochondria compounds. So some people can't, some people can. The biohack in me says, "Huh, what would happen if we could just take the compound that the bacteria make? Wouldn't that be amazing?" We have here with Dr. Singh, one of the guys who's been studying this for seven years. Can you help me explain the discovery process for you saying, "Wait a minute. How did we know this was the one?" Why Urolithin A, which, by the way, is a terrible marketing name? You guys should have some ... Oh, wait. You do. Timeline is the marketing name for it, but Urolithin A. Why that compound out of all the other stuff you could look at?

Urolithin A, why that compound out of all the other stuff you could look at?

Dr. Anurag Singh:

Well, there's a great story behind how that name came. Urolithins were actually discovered maybe back 40 years back in 1980. They were discovered in beavers, in the urine of beavers. So the nerdy professor who discovered it said, "Well, I discovered it in urine." So that's the uro part and he saw them as crystals, so that's the urolith. Now, beavers, you wonder why this discovery was made in beavers. Well, beavers eat a lot of tree bark of oak trees, and these oak trees have a lot of polyphenols, your favorite topic there, Dave. So typically, ellagitannins. So that's how this molecule was first discovered.

Now, Amazentis, fast forward 30 years, Amazentis has been studying ellagitannins and pomegranates for almost 14 years now. We started with the theory that we could bring the deep science approach to nutrition and natural product discovery. So we started by deconstructing the pomegranate because the last 30 years there's been so many studies and health benefits associated with pomegranate.

Out of the hundreds of compounds that we put, you start aging research typically in using worms and animal models, when we put the ellagitannins or ellagic acid, as you were mentioning, on these worms, that didn't seem to be extending the lifespan of the worms, but when we said, "Okay. Let's try these byproducts of the metabolism of the gut microbiome called Urolithin A," and we sprinkled that on the worms and they started living by about 45% longer. That set the alarm bells ringing and was the eureka moment. From there, we gave it old rodents. In just six weeks, we started seeing about 40%-50% increase in aerobic endurance and increase in grip strength by about 10%. The native polyphenol compounds are not doing it.

So that's triggered the whole discovery around urolithins and how we focused and zoomed in and started moving. It was really, as you put it, this postbiotic, the process. You need two biosis to really produce urolithin. You need to eat a right diet. So as you said, you can eat fruits, and nuts, and drink a glass of juice, and then you need your gut microbiome. I can also share, I've tested myself and I don't have. I can drink six liters of pomegranate juice and my body will not produce this molecule.

So we said, "Okay. This is how we're going to move forward. There's a need for supplementation."

Dave:

What would happen if instead I went out and I found some species of bacteria that converted ellagic acid from raspberries or more heavily in pomegranates and converted that into Urolithin A? Could I just take that probiotic and expect it to work?

Dr. Anurag Singh:

Conceptually, it sounds appealing and, believe it or not, we have spent long years looking in that direction as well. It's not easy because our gut microbiome is very complex ecosystem with hundreds of millions of different species interacting with each other and they need to be interacting in perfect harmony to release these postbiotics, which is the way I look at it is the perfect gut health relationship with these microbiome. So it's not one bacteria. It's not one strain that you can isolate and give. It's really got to be multi-species.

So I think you can probably conceptually find that strain or probiotic that could do it, but the process will be so inefficient that the best way, and that's the way we have come up with in the company is to short circuit it and provide the postbiotic, which is Urolithin A directly in a pill or in a food product.

Dave:

So what you're saying is that if someone took a probiotic that was actually stable enough to be delivered to their house and then to make it through the acid in their stomach and it took route or maybe they just stick to probiotic in the other end, which is actually probably a better strategy for a lot of probiotics. It's just less attractive to take a pill that way because it's not a pill anymore. So let's say you could get it to take route in the gut. Then the environment around it, it will be outcompeted by other things unless you have a constant supply of pomegranate juice and there isn't something more aggressive. So it's really a difficult thing to do to say, "How do I balance this stuff?" It's one thing to say, "How do I get what my body considers as enough for me to live a normal life?" like your parents who made it into their 80s.

You're like, "Okay. I want to do better than that." So what you do is you say, "Okay. I want more of this compound." If they had pomegranate and they have the gut bacteria, that's not enough to matter. So now you take Urolithin A as a purified compound and that's something that works for everyone then because it's direct. Unless is there a genetic susceptibility to which pathways for mitophagy are going to be activated by Urolithin A or pretty much it just works?

Dr. Anurag Singh:

Yeah, pretty much it works. It doesn't matter what levels of urolithin, whether you're a producer, a natural producer or not. In our clinical studies, we have both health people who come in and we see great effects on muscle strength and physical performance. So, yeah, it works for me.

Dave:

If you compare a dose of Mitopure, and this is the Urolithin A stuff from Timeline, a dose of that. It comes in a little packet or a pill. How much pomegranate would you have to eat or drink in order to equate that dose?

Dr. Anurag Singh:

Yeah. That's the study we just published. You actually need to eat, drink about six glasses. So about a liter and a half of juice to be equivalent if you were blessed with the natural microbiome to get the equivalent of 500 mg, which is in this food sachet here. So yeah.

Dave:

Wow! So six glasses a day. Having been raw vegan, guys, I know, it's a shameful part of my past. I do my best not to talk about that. I'm embarrassed that I did such harm to my health and I did such harm to the planet by not supporting grass-fed agriculture, but those are different things. I did eat substantial amounts of fruit and lots of pomegranate juice because I had a tree in my backyard.

Strangely enough, my blood sugar wasn't very well-managed because six glasses of pomegranate juice has enough sugar to raise your triglycerides and probably give you fatty liver if you drink that much every single day because fructose is a major cause of fatty liver after alcohol. So that doesn't seem like a good strategy to get mitophagy by overdosing on high amounts of fructose. I don't think it is. That's all accurate, right?

Dr. Anurag Singh:

Yeah. That's perfect. The other thing we saw was, well, maybe if you provide the pomegranate juice as a perfect diet to the people, maybe their microbiome will now see it and start converting. Even when you provide this amount of pomegranate juice with a perfect diet, we do see somehow the microbiome evolving in certain amount of people. From 2%, you can maximum push this percentage. Let's say we studied 100 people. You can have about 40% of the people, 30% to 40% of the people now making it, but those amounts are so variable, so subtherapeutic that you will never really be able to harness the health impact that you will get by direct supplementation. Really, I'm happy to share the paper that we just authored and shared with your audience because I think it makes for a great reading.

Dave:

All right. I'll put that up in the show note links on [daveasprey.com](http://daveasprey.com) because it's fascinating. If you're saying, "Look, I'm not interested in the research, just tell me what to do," well, the bottom line here is the product is called Mitopure and you take a pack of this stuff. On the last podcast I did about it, you can put it in your coffee if you want to. It's heat stable. Just confirm that with you.

Dr. Anurag Singh:

Yeah, yeah. Absolutely. It's very stable. I still take pills from, I don't know, three, four years back and I still get great absorption variability. So it's very stable.

Dave:

Okay. Good. So you can do that. I will tell you, I got tired of raspberry flavor in my coffee. I like my coffee with butter. So the fact that Mitopure makes capsules is convenient for me, but the raspberry stuff is nice and it's going to some other prebiotics in it, I believe, as well. So that's a good thing.

I sent the powder out to people who are in the Dave Asprey Box. Go to [daveaspreybox.com](http://daveaspreybox.com). Every quarter, I send out a box full of cool stuff worth way more than you pay for it. So people in the Upgrade Collective who are members of the box have definitely given it a try. I'm seeing all the comments here saying, "I like it. It's the real deal."

I do have to say I take it the vast majority of days. Every now and then I miss something, but I want to know, and in fact, several members are asking, what's the best time of day to turn on

mitophagy? Because we know a lot about circadian timing of vitamins, vitamin D in the morning, magnesium in the morning and maybe at night but certainly in the morning. When do I want to do Timeline? Is this during a fast even though it has some raspberry powder, end of a fast, morning, night? What's your take?

Dr. Anurag Singh:

Yeah. So all that clinical studies are done where we see great health improvements in muscle strength and mitochondrial health, they're done first thing in the morning. So participants usually take it first thing in the morning in a fasted state just before taking their breakfast. The idea is that you peak the absorption if you know the kinetics of absorption of this vehicle molecule is it peaks about six to eight hours after the intake. So it's giving max hitting the peak when you're at the peak day activity in a day. Yeah, fasting is a little overnight fasting. It's also known to be inducing autophagy and mitophagy. So yeah, take it and amplify the Mitopure in the morning.

Dave:

So during a fast?

Dr. Anurag Singh:

Yeah, during a fast it will work. Yeah.

Dave:

I think there's, what, 10 calories or something in a packet. So it's enough.

Dr. Anurag Singh:

Yeah. It's really nothing. I think it's hardly got any sugar. So I think probably-

Dave:

I don't think it's going to raise insulin in any way that would shift mTOR. I haven't measured it, but it's such a small amount. See, I have people who are saying, "Wouldn't it break a fast?"

Guys, it doesn't look like. I don't think it would, but I haven't measured with one of my glucose meters. I've taken my coffee during a fast and seemed no difference, but I wasn't specifically setting just that.

Dr. Anurag Singh:

That's with the powder. We also have the pills as you said. You can pop two pills.

Dave:

That won't break a fast with the pills. That's what I do now after I used all the packets that I had. I had six-month worth of packets. To be really clear, this is one of the superstar antiaging supplements that I plan to be taking daily for a long period of time just based on the strength of the research. I do about 100 pills a day, 150 sometimes if I'm traveling. Some of those are because they're large molecules like magnesium or glutathione or something, but definitely this is in my stack, and I'm expecting it to be there for a very long period of time because of my aging goals. So I basically only talk about stuff that I think is worthwhile and that I'd be willing to do.

I want to know something. You've done seven trials on this stuff now?

Dr. Anurag Singh:

We are on our sixth trial.

Dave:

You're on your six. Okay. Seven years, six trials. Okay. How are you measuring mitochondrial health? At Upgrade Labs, I'm helping people train and improve it, but measuring it is really a pain. So what's the mechanism there?

Dr. Anurag Singh:

It's not easy from a scientific or clinical assessment. So we measure it two ways in our trials, the mitochondrial health. We either do some biopsies in the muscle, which is, well, I can imagine it's not the easiest to do in real world, in clinical settings.

Dave:

Yeah, it's going to hurt.

Dr. Anurag Singh:

We look at mitochondrial gene signatures. We look at respiration and live muscle. So that's what we do. That's, let's say, the most validated way. Then we do what is called as magnetic resonance, spectroscopy, which is noninvasive, which is basically you go in a MRI-like setup and you exercise in a lumbar MRI and as you exercise, your ATP levels in that muscle that you are studying or the brain will go down. Then you see how fast the ATP is coming back and how fast it comes is really a measure of your mitochondrial health.

Involves heavy machinery, involves having magnetic scanners, that's seven Tesla and all. The other old school way is to look at biomarkers, which is something we have been investing a lot of time to study. We've been looking at a panel of molecules in the blood called acylcarnitines that basically are involved in fat oxidation. So they are defacto markers of good mitochondrial health.

If you really had to go at a high level, you could look at your VO2 as well as a defactor marker.

Dave:

That's what we do at Upgrade Labs. We've got some proprietary tech for that, but that's a pain. You're on a bike. You have to be fasted, breathing through a mask. It's not one of the things you're going to do unless you're really a nerd, right?

Dr. Anurag Singh:

Right, right. Yeah. So I think there's still a long way to go to crack that holy grail of what's the perfect biomarker of mitochondrial health, but, yeah. I mean, in real life, you'll know it from fatigue and energy levels down to your VO2 and then at the molecular level to these biomarkers I'm just mentioning.

Dave:

Long time listeners have probably heard me talk about acetyl L-carnitine as something you might want to take when you're on the Bulletproof Diet or you're switching to a high-fat diet or you just want

mitochondrial function. You mentioned members of that family. I think that would probably change test results if people are supplementing that, right?

Dr. Anurag Singh:

Yeah. That's what we see as well in our studies that totally some of them will also get published very soon.

Dave:

Okay. Very cool. What about our urine organic acids? Useful?

Dr. Anurag Singh:

No. We haven't really seen them. We look at some mitochondrial Krebs cycle metabolites in addition.

Dave:

Succinic acid, things like that.

Dr. Anurag Singh:

Things like that. Yeah.

Dave:

All right. So I'm wondering how many of our audience is completely like, "What the hell are they talking about? They're bored," or I mean, [inaudible 00:30:39] and doctors jumping up and down in their cars is going, "Someone finally said succinic acid," but it's fascinating because I'm going a little deep with you there. I've read a major New York Times bestseller about how to enhance mitochondrial function, yet measuring it is always looking at the shadow of it instead of looking at it directly, looking at evidence that was there, looking at smoke instead of the fire. In fact, that's the best analogy I can think of. Okay. You're saying the best way is those acylcarnitines.

Dr. Anurag Singh:

Yeah, from a biomarkers. I mean, the best way is ultimately to look at ATP in real time with imaging and those tests I think from going from imaging to something that is point of care will take some time.

Dave:

All right. I think for all of our listeners, I don't have an answer for you guys about mitochondrial health, but when you have a clinical researcher with a massive NMR equipment, they can do it or you have some of the gear we have down in LA at one of our research piece of equipment for VO2. It's not VO2 max. It's a different algorithm. So it's hard to do it is the short answer, but the easy way is how do you feel when you wake up in the morning? Do you have athletic endurance? Does your brain work all the time? If so, you're mitochondria are probably working better.

Here's my question for you about Urolithin A or Mitopure. There are some supplements that I'll take that are direct stimulators of ATP creation and mitochondria and you feel it like, "Yeah." Even MCT oil changes the amount of electrons available because it carries more than sugar. So you're like, "All right. I've got myself back today. My brain is where I want it to be. I don't get a buzz from Mitopure." Do you? How long does it take to feel a change in mitophagy because if you change a light bulb and you

have a million of them and you change 1% a day, you're not going to notice a change in brightness maybe ever because it's a slow change. What's the rate of change when people start using Mitopure?

Dr. Anurag Singh:

Yeah. So what we have seen in our studies and then I'll mention some of the folks I chat with who are on the product. So in our clinical studies, around one month after or four weeks after we start noticing biologically development changes. So changes that you would expect from exercise regimens of many years. That's the level of impact on mitochondrial gene signatures of biomarkers. Then about two months, we really start seeing about 10% improvements in VO2 and in things like muscle strength would take a little bit longer than four months because physical performance and improving muscle strength takes time. It's not on/off that in a week you will improve your muscle strength. It's constant remodeling. You have to clean the waste out of you to create new mitochondrial biogenesis and you need to create those mitochondria need to be then efficient. So it takes about I would say about a couple of months.

Dave:

Okay, a couple of months, and this is what daily use of the recommended dose. Is it body weight-dependent? The reason I'm asking is right now, given how ripped I am, I'm around 230. I vary between 210 and 230 depending on what experiments I'm doing and other stuff like that. I have very large legs. So it's easy. I just do a few squats every day and magically I put on muscle, but it's all in. It just makes my pants not fit.

So most of the supplements I take, they're meant to be a safe dose for a 90-pound woman, and that's what we have to do at supplement companies. So I usually double dose things. Should I be doing that as a larger person with my ... Let's see. My BMR is something like 2,900 calories a day. Does that mean I just need a higher dose or is it you take it and it work regardless of your body weight?

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My BMR is something like 2,900 calories a day. Does that mean I just need a higher dose or is it you take it and it works regardless of your body weight?

Dr. Anurag Singh:

Yeah, it's a good question. Actually, it's a great question. We have seen impacts at the 500 mg dose on muscle strength and on mitochondrial health and cellular health. Now, we have done what is called a dose escalation study. So you take a quart of people, you give them low dose and then you raise the dose, and then keep on doing. So we have done that till two grams. The best data we have is actually on one gram, which means double the dose.

Dave:

That's what I was doing just because I always double the dose. Okay.

Dr. Anurag Singh:

Yeah. So that improves mobility. You have more bioenergetics. You're walking better. As I said, the VO2, 500 mg and one gram is also very safe dose. We have data on this molecule that you can up it. There is no limit to it where you will get a safety signal. So I would say, yeah, if you want to try out upping the dose, sure, by all means. I take double the dose myself.

Dave:

You take double the dose as well.

Dr. Anurag Singh:

Yeah.

Dave:

This is a very different situation. Years ago, I interviewed a guy from Vanderbilt University. I call him Dr. Nicotine. He did the first study of pharmaceutically separated pure nicotine versus using tobacco. He was looking at Alzheimer's disease studies. That came out in 1986 and showed a reversal of Alzheimer's disease. My hypothesis would be probably through PGC1A effects, but who knows? Maybe it's for some other reason, but at the end of the interview, I said, "Have you ever used nicotine? What's your favorite form? Are you taking some now?"

He says, "No, I've never used it. I want to keep my research pure."

I'm like, "No. If you believe it works after 25 years, I feel like you really should be doubling down on it," which is exactly what you're doing. You're saying, "Okay. I'm doing it."

Dr. Anurag Singh:

Yes, and one of the markers we actually look in the muscle is this PGCA, and in one month, we have actually published that this molecule can increase the expression of PGC1A, which means biogenesis is already starting to happen. So yeah.

Dave:

Wow! Guys, if you haven't read my books or you just didn't remember it, PGC1A is what happens when you exercise. So it's an exercise mimetic thing. Things that raise PGC1A, funny enough they make you lose weight, they suppress hunger, and they're generally good for you. Although too much nicotine is probably not good for you, but a little bit probably is. So reminding me I should stick a patch on or chew some gum or something, but I'm not going to chew gum on the show because it's gross. All right.

Are you up for a question from the Upgrade Collective? Lisa has a good one that I've been working here.

Dr. Anurag Singh:

Sure. Absolutely.

Dave:

All right.

Dr. Anurag Singh:

Shoot it.

Dave:

Chris, let's patch her in.

Lisa:

Okay. So I'm wondering, is a higher dose of Mitopure better for mold toxicity or any mast cell symptoms one might have?

Dr. Anurag Singh:

Good question. We have not studied, let's say, the immunological effects of Mitopure. This is an active area of research. A lot of academic groups since our publication have started studying it. They've been studying models of IBD. They've been studying models of neuro degeneration and this at least a model of IBD they looked at they saw that it had an anti-inflammatory effect. So hypothetically, I would say probably yes, but we have not done any clinical studies or looked into that direction.

Dave:

Thanks, Dr. Singh. The bottom line I would say from everything I've studied is that if you want to live a long time and you want to turn off inflammation, inflammation is the opposite side of the coin for mitochondrial function. So when mitochondria work better, you have less inflammation, almost by definition. Then to make them work better, stop using toxins that directly affect mitochondria and make sure that the weak ones get the hell out. Mitopure is that latter part, but as you do that over time, of course, athletic performance is going to go up because you're doing a better job of turning air and food into electrons, and that means your immune system should work better, too.

Dr. Anurag Singh:

Yeah. Immune cells of mitochondria, too. So we just chose to study muscle because an active muscle has about 2,000 mitochondria. So it's just the most active organ or cell in our body, the muscle cell that it requires ATP and consumes ATP at a higher rate. Immune cells on the other hand, about 200 mitochondria. So anything that is having an impact on mitochondria mitophagy is going to be irrespective, just not muscle cell is going to have an effect on other cell types, too.

Dave:

In my mind, the No. 1 thing you can do at any age to either age backwards or not age and perform better is mitochondrial enhancement because it seems like even mitophagy itself, once your mitochondria start working a little bit better maybe because you took some compound that help them that wasn't for a mitophagy, you have to have enough electricity to run the body and enough electricity to rebuild the body. So if you kick your energy levels up a little bit maybe with acetyl L-carnitine, maybe with D-ribose, anything like that and you have Urolithin A or Mitopure onboard, the body says, "Oh, now I have enough energy, too," and then it says, "All right. What's the repair system that's next on the rung of priorities that it has?" It's a relatively simplistic model, but at the end of the day when you pull out all the network effects, it seems like that's what the body does like, "This one was more important than that one. Let's fill that part of the waterfall and then go up to the next one."

So I feel like you want to have enough energy to build new mitochondria instead of just run weak ones. So there's a little bump that's required, which maybe something like combining fasting with this so you have some ketones present. Does this seem like a good strategy? I know you probably haven't studied that.

Dr. Anurag Singh:

No. In a lot of studies that we published, actually, not in clinical studies but in our animal models and worms that we're fasting, this actually increased the autophagy. So fasting induces autophagy and adding Urolithin A to that regimen actually had a very additive effect that was shown in this beautiful

Nature Medicine paper, and exercise would be another way. Exercise is another way to stimulate mitophagy. You just need to be doing it regularly.

So that's where I see, and that's why we are actually running studies now in athletes where we are starting to ask the question, "Can we actually take high performance people, people with VO2s of 70, can we add this to their regimen and can it help boost their performance or most importantly, their recovery because training does have an impact. Over training sometimes has an impact on mitochondrial health, too.

Dave:

It's fantastic. So you've got to get a stimulus in as well. So you should probably sprint every now and then or do some squats or whatever high intensity interval or for cardio endurance specifically, even that it seems to be that high intensity interval training works followed by longer walks or very slow jogs. So if you are doing any of those sorts of thing for an endurance event and you're taking Mitopure, you're likely to over the course of a couple of months see some improvement in mitochondrial function even if you already a pretty good athlete.

So you did a study with a very well-known scientist, well-known amongst scientists, Dr. Louise Burke, who spent 40 years as a sports dietitian and has 350 papers published and has written a few textbooks on sports nutrition. What did you guys find when you collaborated on the latest research you've done on Mitopure?

Dr. Anurag Singh:

Yeah. So this is an ongoing study, Dave. This is a study that was designed beautifully by Louise. She came to us and said, "Well, a lot of elite athletes, runners, triathletes, typically, they go before a big race, they do training, and sometimes they have to do multiple races in an active season, and they struggle to maintain their level of performance and so recovery is a big issue to the muscle recovery and to maintain their peak performance from race to race is a big issue."

So she said, "Well, I think being on Mitopure could help these athletes potentially recover faster and maintain, and the way it could do it is through mitophagy, recycle the waste and the toxins accumulated by over training and overstimulation of the muscle machinery."

So this is what we are testing. We don't have the final results yet. We are dealing with COVID-19 throwing a spanner in some of the clinical research programs, but, hopefully, early to mid next year we will have great data. This is being done in Australia with really Olympic-

Dave:

Oh, you pick the worst country ever except for Canada to do anything. Okay. Your hypothesis for this is one that made me happy that you're doing research on it. It was that over training in athletes induces mitochondrial dysfunction. I think I experienced this when I was a younger person. I was maybe 24. I had weighed 300 pounds and I said, "I'm going to work out six days a week, an hour and a half day," and I'd max out all the machines at the gym except for two and then hop on the treadmill with weights at an angle, in a weighted backpack. I said six days a week, and went on the low-fat, low-calorie diet. I didn't lose any weight over 18 months. I got stronger, but I think I had even worse mitochondrial function because I just didn't do any of that recovery stuff. It's one of those things where something that's good more must be better and you do it until you're exhausted.

What are you seeing around over training and do you think that you've proven the hypothesis so far? I know Mitopure is helping with that, but did you find a result that you could say, "Yes, 100% clear that that's a problem"?

Dr. Anurag Singh:

Yeah. So this is something that is being investigated a lot not by us, but by a Swedish group who recently published a very high impact paper in the journals of metabolism, where they took athletes and they kept on adding training regimens week after week, the intensity of their training increased. Over time they, of course, with any training, they saw improvements in mitochondrial health, but after a while, the system started to crash and it's been known this is called over training. Some folks call it overreaching. Some call it plateau, whatever.

What they found was that this over training-induced performance was because of poor mitochondria function and that was just not offsetting performance. It was offsetting the athlete's metabolism, especially they had higher blood glucose peaks after. Then there was a recovery period after which where the athlete stopped training and then the body recovered, and they were back, too. What was very key was this window where athletes who are over training who had a performance dip and that was ascribed to a mitochondrial dysfunction.

Dave:

Very, very interesting. So we get mitochondrial dysfunction from overexercising. Interestingly in that study, it also decreased glucose tolerance, and a lot of people who are listening are going through that where they say, "Okay. I understand. I don't want to have high glucose, but these are mitochondria that are so damaged or stressed that they can't actually handle trigger, which they should love," right? So it's a disrupted network, you could say. They found this in free living elite endurance athletes.

I've said for many years now that endurance athleticism isn't a good way to live a long time, but there's one or two studies that show ultra-extreme 100-mile runner types, if they can do without getting injured, which is a very small number, but that they do have lengthened telomeres. Have you seen any association between Mitopure and telomeres being longer?

Dr. Anurag Singh:

Honestly, no. We have never looked at telomere biology. One of the reasons is we have such a specific mechanism of action through mitophagy and renewal of these mitochondria that, yeah. Honestly, we haven't explored that biology.

Dave:

I don't think you'll see a difference or I don't think you'll see a lengthening from what Mitopure does, but if you took Mitopure for quite a while and someone had more free electricity for repair processes, I think you probably would see a slowing of the shortening of the telomeres.

Dr. Anurag Singh:

Maybe. I think you'll need to do long-term studies for that.

Dave:

Yeah. Those are expensive and hard to do, and probably will never be done. That's one of the challenges for all the antiaging stuff that I do is saying, "Well, here's a mechanism of action. We understand it

pretty well. We know the basic direction. So if you had to bet at which one of these is going to make you live longer, I'll take the bet that I think it's most likely. I could be wrong, but given the alternative, which is eating hotdogs and drinking diet soda, I'm pretty sure I'm winning." So there's always that.

Here's a from Hara in the Upgrade Collective, who's put it through in our little chat window here during the show. She's wondering whether you could combine this with breathwork practices, which are reducing oxygen and increasing carbon dioxide. Any thoughts on breathwork plus Mitopure?

Dr. Anurag Singh:

Potentially yeah. Breath analytics could be utilized. I mean, that's how a lot of exercise tolerance studies are done looking at the gas exchange and that's how we look at VO2 levels, but I think the question is referring to certain breath biopsies.

Dave:

Pranayama or Wim Hof exercises or any of the other things like James Nestor has written about recently that there's a lot going on with carbon dioxide versus oxygen levels on retention.

Dr. Anurag Singh:

Yeah. This is a, let's say, upcoming field of research, but we haven't looked into it, Dave.

Dave:

You can always count on the Upgrade Collective to say, "How do we combine all these cool biohacks that we've learned about to get the most effects?" Another question, well, actually, guys, it's a question about how do we make Mitopure available for more people, but I don't think asking research scientists about that is the right thing. You're not in charge of pricing, packaging, and distribution. So is it easy to make, though, as a molecule or are you mostly just getting it already made and then you're saying what it does and humans and animals and stuff like that?

Dr. Anurag Singh:

Well, yes. It's not too difficult to make with the right chemistry knowledge, but one of the things, and this may interest your audience, one of the things we're developing is a Mitopure Challenge Test. So it's a kit. It's a consumer health kit that looks like this.

Dave:

Oh, cool.

Dr. Anurag Singh:

So you have to take a small blood prick test in a card called Before. You just prick with a lancet and you put some blood spots. You can drink juice as well. You can drink juice or eat a bowl of nuts and you can know if you are actually a natural urolithin producer. Then you can take this one sachet and then repeat the test called After with a few blood spots and send it to our lab and we'll be able to tell you if you are a natural producer and the delta difference you will get from just taking this.

Dave:

Wow!

Dr. Anurag Singh:

So this is a test. We are actually running a home base study. If your folks are interested, we can share the link and they can try the beta version.

Dave:

Okay. I will send this out to the Upgrade Collective members. There's all kinds of discounts and other cool things that you get when you're in the Upgrade Collective. By the way, if you're listening going, "I want to be in the live audience," our [upgradecollective.com](https://www.upgradecollective.com). Sign up for my mentorship and membership group. It's intriguing. You guys haven't even sent me one of those test kits yet, but I have great respect for that. The idea that if you're taking a vitamin and you can test that it's working, that's a really good thing to do so you can see if it's worth it for you. In fact, yeah, everyone's exploding with excitement right now on our group chat during the episode.

So that study I'm excited and I'll make sure-

Dr. Anurag Singh:

Yeah. Happy to send you one. Happy to send you. We just got the first 200 beta kits. Happy to send you one and if you want to participate, send your samples to our lab and, yeah.

Dave:

Okay. Does it matter if I take Mitopure with a larger amount of prebiotic, a bunch of acacia gum or something or with fat or with protein? Do any of them help with absorption?

Dr. Anurag Singh:

No, not at all. Actually, in our first human studies, we actually tested this. We gave it on an empty stomach in a fasted state or with a high protein and in a yogurt matrix to see if high protein and the levels we get in the blood are identical. So in fact, we now even have a product with high protein, 28 grams of protein plus Mitopure 500 mg because with the idea that protein builds muscle mass and then the Mitopure gives you better energetics and strengths. So now actually it's, I think, beneficial if you combine them.

Dave:

Okay. Got it. So there's really not stability issues. I mean, you could take it, you can mix it into hot coffee and it works fine. You can take it with protein or anything, so the absorption rate is pretty much as if your gut bacteria had done it. When I take Timeline, I know, let me rephrase that. I know that there are certain compounds when you take them they cause your gut bacteria to make more of them. Glutathione is one of them in some people and things like butyric acid. If you take a butyric acid capsule, you're more likely to make gut bacteria that make butyric acid. So part of my antiaging strategy is I'd like the little manufacturing plants called My Microbiome to make the good stuff and not the bad stuff. It's easy, but, of course, you don't have much control. It's a very complex system. It's like managing ecosystem. It's hard to do. What a great job we're doing on the planet right now. Monsanto, I'm talking to you. I mean, Bayer.

Aside from all of that stuff, what about just taking Urolithin A for a while and then having your gut bacteria make more of it and actually make those producers of Urolithin A and then taking a month off, right? There are people in the Upgrade Collective who are on different budgets, and some people

are saying, "Well, can I pulse this? Is there benefits to pulsing it? Can I teach my bacteria?" So talk to me about pulsing, cycling, and training your gut bacteria to handle ellagic acid.

Dr. Anurag Singh:

It's fantastic. There's a lot of questions hidden in that one question.

Dave:

Sorry. Yeah. I'm a bad interviewer at this point.

Dr. Anurag Singh:

No, no, no. Butyrate is a great example, by the way. Butyrate is a perfect example of a postbiotic. So butyrate is good for your gut health. Similar analogy is Urolithin A is great postbiotic for your muscle and mitochondrial health with the access of microbiome and mitochondria.

So on the pulsatility, we have not done once a day or twice a day what's the impact on absorption. This is something that is currently in the works, and we're planning that longer term studies, longer than four months, we haven't done as well. What we have done is in one of our studies we have looked at the gut microbiome of people, well, a couple of studies, we looked at the gut microbiome of people who actually make it versus don't make it. Definitely, the gut microbiome of people who produced Urolithin A is much richer and more diverse compared to those who don't make it. What we've seen is over time if you supplemented over four months, for example, and then again look if the gut microbiome suddenly changed. No. The answer is you don't really. It's a postbiotic, so it's the end result of a healthy microbiome, but it doesn't really induce big changes on the gut microbiome per se.

Dave:

So it's a postbiotic, but it's not one that causes a change in the behavior of gut bacteria. It's only just bypassing them to give you the benefits as if you had stupendous numbers of the good ones making Urolithin A. So what would happen if I was on Mitopure for 10 years straight?

Dr. Anurag Singh:

The analogy I'd like to give is I always show a slide where I show muscles of exercising people, who have been exercising all their life and how they're looking at 70-80 years old, and then I show in parallel four-week intervention how muscles look like and they look almost identical. So the question is, really, how long should I be exercising? Are we hitting the same biology, same pathways? Now, of course, we have not done studies longer than four months as you mentioned over a year or two years, but it's a nutrient.

To make another analogy, it's like vitamin C of aging. So will you stop exercising? Will you stop eating healthy diet? No. You will take it. The kinetics, the way it works as I told you, it has a half-life, which means that it disappears from your bloodstream in about a day. So it's daily administration that you need to maintain enough what we call as therapeutic levels in the blood.

Dave:

Okay. Got it. That's a pretty clear answer. So guys, what you'd want to do is take it often and I take it pretty much straight all the time because I think the research is there. The fact that you've seen improvements in exercise performance is a really good sign and that you're doing really hard core science, way more than you would see for a typical supplement, which has me excited.

So I think that you're looking at a foundational thing, and if someone said, "All right. I'm going to do this for one month and then take a month off and do it for a month. Is it better to do that versus two weeks on, two weeks off?" There are people on budgets.

Dr. Anurag Singh:

Yeah. I think you have to stick to the first two months at least to see the impact, and then the question is, "Can I lower the dose or up the dose or how should I switch it?" The honest answer, I mean, we are a science-driven company, so we still need to-

Dave:

You don't know.

Dr. Anurag Singh:

We don't know. So we need to-

Dave:

I understand, sir.

Dr. Anurag Singh:

We need to do more trials and we need to add more evidence on the plate.

Dave:

Here's what I would do in answer to the question from our Upgrade Collective member who asked it. I would do it for two months the way we just learned from Dr. Singh. Then if you have to take a month or two off, great, then do it for two months, right? So you may go up, you may go down, you may go up, you may go down. If I've learned anything about keto by testing it out before I wrote the Bulletproof Diet and all its cycling is always at least okay and usually better than steady state.

So in this case, I think steady state is a good idea for Mitopure, and that's what I'm doing, but if you had to do it, I don't think cycling is going to cost more harm. So you're saying, "All right. I had a period of great mitochondrial refreshing and a period of less good, then a period of great good," and then you saved some budget there, which is okay, but my recommendation would be just do it all the time that's within reach and your goal is to live a long time.

My final question for you, Dr. Singh, what about cognitive performance? I mean, into my nootropics, have been for years, and I got 40 years of Zen, where I have people coming doing very high-end brainwork. Have you done any studies or seen any anecdotal results around measures of neurological performance versus just physical performance?

Dr. Anurag Singh:

Great question again. So there's a lot of research going on around this molecule. Actually, Buck Institute of Aging in California just got a multimillion grant from the National Institute of Health to study the effects of Urolithin A on the cognitive aging and how it can reverse some of the neuronal circuitry to look youthful. So we are actively looking at it, but we're keeping our eyes and ears open for exactly feedback like this because brain cells also after muscle cells have the highest number of mitochondria that decline with aging. So yeah.

Dave:

You know what would be really cool? They have these places where you can go and you can bet on almost anything like an election outcome, just any random thing you can bet on, and it turns out that betting markets are ridiculously good at predicting outcomes. We need a scientific betting process because having written a book on cognitive function improvements via mitochondrial function, I'd put a lot of whatever cryptocurrency, gold or rapidly declining fiat currency on a bet that that study is going to show positive results. In fact, if we had a scientific betting market, we could probably just quit doing science and we'd all just bet and we get the same results. What do you think?

Dr. Anurag Singh:

I think you're on to something there. Probably it's not a bad idea to make the scientists more aware of how they can commercialize stuff, but I think I'll talk about my experience there. As I mentioned, I've been taking it for about a year. I'm a busy guy with young kids who wear me down, but since I have taken the product, here, I'm at 8:30 at my time talking to you and I feel more attentive. I feel more energy. So energy is just not in the muscles. So I think you're probably right. Time will tell. Research will tell in the long-term, but probably it's an area to focus on and do some research with Urolithin A or Mitopure in neuro cognition.

Dave:

Okay. So there's more to be found there. I thought that was my final question, but Joan just jumped in. Thanks, Joan. Right at the end. Great question. "Any changes in sleep from Mitopure that you guys have come across?"

Dr. Anurag Singh:

No, but we have heard some, let's say, anecdotal feedback that people are seeing impact on waking up more fresh and this does have an impact. This is, again, something we need to look further in, but that's the beautiful aspect of now seeing it go into real world is now we're getting these great feedbacks and now you can hear the consumer feedback and actually see where to focus your research beyond just focusing on muscle health. So yeah, this would be something on the top of our research table.

Dave:

There you go. If you can focus on muscle stuff, you should look at erectile dysfunction and hair growth. If you can just conquer those markets, you guys are going to be kabillionaires. Unfortunately, if you look at where people spend their dollars, that is a ridiculous percentage of it, and probably Brazilian butt lifts should be in there as well, but I'm glad you're focusing on aging and the performance you're doing because those actually matter more and those other things are very far downstream outcomes from having good health, but that's where people, they want to put their money there first.

Well, Dr. Singh, thank you for the work you're doing with Mitopure. Guys, [timelinenutrition.com](https://www.timelinenutrition.com) and you can use code `UPGRADE10` and they'll give you 10% off the plan of your choice. I'm on the whole yearlong subscription plan. So it just arrives every month. It comes on a nice case and all that kind of stuff. I just think it's worth your time if you're on either an athletic angle or an antiaging angle or potentially we don't have proof, but I'd bet on it, a neurologic, I want my brain to work better angle or you just want mitochondria that are stronger than your neighbors and you could just be a mito geek. That's cool, too. So [timelinenutrition.com](https://www.timelinenutrition.com) and it's code `UPGRADE10`. Dr. Singh, thanks again for being on the Human Upgrade.

Dr. Anurag Singh:

It was an absolute pleasure, Dave. Thank you for having me.

Dave:

You're listening to the Human Upgrade with Dave Asprey.