

How to Get Fitter Cells, Stronger Muscles and a Longer Life – Timeline Nutrition with Dave Asprey – #772

Announcer:

Bulletproof Radio, a state of high performance.

Dave Asprey:

You're listening to Bulletproof Radio with Dave Asprey. Today is going to be a really fun show because we're going to talk about Urolithin A. Okay. Maybe you don't think it'll be fun, but trust me it will because there is a huge amount of new knowledge from two experts who know a lot about plants and how plants interact with our cell biology.

Dave Asprey:

The first of the two has a background in cell and molecular biology, biomedical engineering. His name is Chris Rinsch. He's a PhD, 20 years of experience. He's written original publications that have been published in science journals about Urolithin A. This stuff affects muscle function, cells, and mitochondria, and you guys know I'm kind of a mitochondriac here. Our second guest is Navindra Seeram, a PhD who's a professor and chair of the biomedical and pharmaceutical science institute or department at the University of Rhode Island. He runs the Bioactive Botanical Research Laboratory figuring out what medicinal plants and their compounds can do against chronic human disease. Welcome to show, Navindra and Chris.

Navindra Seeram:

Hey, thanks for having us.

Chris Rinsch:

Thanks, Dave.

Dave Asprey:

I want to start, Navindra, it's really interesting that there's a whole university department about this, how do we get compounds from plants and separate them out and do things like that. What got you into plants?

Navindra Seeram:

My department, as you said, the Biomedical and Pharmaceutical Sciences Department is within the College of Pharmacy at the University of Rhode Island. Now, people are probably wondering what is nutrition and plants have to do with pharmacy? Interestingly enough, the field that I work in is called pharmacognosy, which is, if you will, you could think of pharmacognosy as being the mother or the father of pharmacy. It's where the discovery of drugs started since ancient times. My background, I'm a third generation East Indian, as my name, you could tell, Navindra Seeram. But I grew up in the British colony of Guyana, which was British Guyana, and it's now Guyana since independence. It's in South America. But being a third generation, and growing up in a very poor third world country where there is not access to medicines and physicians like we know over here.

Navindra Seeram:

I'm in the United States. I've been here for many, many years. So, when we were kids growing up, and we had a toothache or a tummy ache we'd go to mom and grandma. They had an Indian origin, and say, "What can we take?" And they would say, "Take certain plants. Make a tea or chew on it," and lo and behold, the plant works, or worked. And so, from growing up, from my time as a boy growing up, my interest was very piqued in what in plants are actually responsible for these effects, powerful effects that we know in humans, and from them I progressed.

Navindra Seeram:

I did my PhD in the beautiful island of Jamaica, Kingston, Jamaica, at the University of West Indies, and then I migrated to the United States. I did a quick postdoc at Michigan State, spent some time at UCLA. I'm sure we'll talk about the pomegranate when we get back to that. And here I am at URI still trying to understand what are the bioactive constituents in plants, and how they can benefit human health? So, a long answer to your short question, but I'm sure we can come back around, Dave.

Dave Asprey:

I have a belief system that's crystallized over the last 10 or so years, and I want you to poke holes in it, or agree with it. But this is not something I've really talked about publicly, but you're the perfect guy to ask. I think most plants want to kill you. In fact, we know that because if you just pick up a plant in your backyard, and eat it, you're not going to like your day. So the process of cooking is largely or at least in part to... or processing, that includes fermentation, all that is to remove a bunch of the toxins in it. I'm seeing extraction methods, whether they're pharmaceutical, or alcohol extraction, all that, it's just a way to remove the harmful group of stuff that we can tolerate, but isn't good for us and amplify the good stuff.

Dave Asprey:

So, I'm looking at the pharmaceutical stuff you're doing is just modern cooking, in a certain way, which allows us to take plants we might not want to eat a lot of it. But this one thing in the plant we would benefit from rather than as a pharmaceutical science, really, it's just advanced way of removing the bad, so you can leave the good. Is there good thinking there or am I oversimplifying?

Navindra Seeram:

There's good thinking there, and we've been here different programs. I mean, a lot of times to delve into this, but you were right. Sometimes we're extracting, we're doing cooking to maybe, again, as you just said removing or maybe increasing, fortifying, increasing that bioactive constituents or group that we would want. A good example from the Caribbean where I grew up, again, is cassava, also known as yuca. This is a very toxic plant, and it [crosstalk 00:08:09]-

Dave Asprey:

You have cyanides in it.

Navindra Seeram:

But somehow the people figured out in ethnobotany and ethnomedicine that by cooking cassava and throwing away the water you can get rid of the cyanogenic glycosides. And then, you'll consume the food for its starch. So humans and plants have co-evolved for centuries, and you're right. Plants don't care about us. They're obviously protecting themselves. And they produce these natural products or these secondary metabolites for their competitive advantage. Well, we could argue that maybe as plants

and humans co-evolve that a plant became very colorful, or it has its beautiful berries because humans can see color. So, eat me, cultivate me, so you can disperse off my seeds, and you can make me procreate and keep on going. Maybe that's one thought.

Navindra Seeram:

Certainly you have toxic plants. But certainly we have these edible plants, which humans have been cultivating and consuming for centuries. And to get back again to the question, that by consuming these natural products, these are hardcore chemical compounds. These are not vitamins and minerals, and fats, and carbohydrates, and proteins. These are... If you look at their chemical structure, these are really drug like type molecules. And when you think of our body of we're consuming these molecules over time. Our liver getting to do its thing in terms of detoxifying and our kidneys, and excluding, and again our gut microflora.

Navindra Seeram:

Converting some of these natural polyphenols that are found naturally in the plant into further bioactive constituents, which I think is really where the rubber meets the road.

Dave Asprey:

When we talk about plant based compounds, like you said, there's so many of them, and your caffeine and nicotine are amazing. By the way, smoking is bad for you, in case anyone's misconstruing what I'm saying there. I just like the anti-Alzheimer's effects and the cognitive enhancement effects. But polyphenols as a class are something I wrote extensively about in my anti-aging book because there's just so much evidence there. But a lot of the plants that contain polyphenols have stupid amounts of sugar, or other toxins that I don't really want to get in large doses in order to get the polyphenols.

Dave Asprey:

And that's where the line between medicinal plants and herbs and food plant starts to get really blurry to me because I'd love to have half a gram of this compound, but I don't want to eat 40 pounds of foods to get it because that would be hard. Are we at the point now where you feel like we know enough about these colored compounds and foods that it's safe to say, "You have to eat the rainbow and get all the lectins and all the other bad stuff. You could just take a pill that contains all the good stuff from the rainbow and throws out all the bad stuff with no sugar." Are we there?

Navindra Seeram:

I think we're close there. The cutting edge instrumentation that we have throughout the world, and with science is the ability to again as you just said, to enrich in certain bioactive constituents and remove some of the unwanted constituents within the plant foods. For example, I'm just going to throw it out as an example. Cranberry juice, people may not like a taste or if you're having cranberry juice with the added sugar you may not want that added sugar but is there a cranberry extract that could deliver the bioactive constituents in cranberries which are potentially going to protect urinary tract from being infected? And that is-

Dave Asprey:

Why do you say potential there? Is that because you're academic and you just have to say everything is potential?

Navindra Seeram:

Yes.

Dave Asprey:

We know D-mannose stops bacteria from sticking to the lining of your urinary tract, right?

Navindra Seeram:

But the FDA this last July just allowed a qualified health claim for cranberry. You can check it out.

Dave Asprey:

Okay, there we go. So now we can say it's real because the FDA said. Okay. I got you, Navindra.

Navindra Seeram:

[inaudible 00:12:07], thank you. But again, yes, delivering the bioactive constituents in a calibrated form with standardized, and you know what it is without the unwanted constituents, I think we're there.

Dave Asprey:

You think we're there? I'm feeling that way too. You can get almost any polyphenol separated out you want. A lot of times you can get them in a supplement that you want. And also knowing which ones and in what ratio, it feels like there's a bit going on. But hey, if you eat a salad, you don't know which polyphenols at what levels you got in your salad either. So, it's no worse than the current situation of just eating some random stuff because a health expert in the '70s said eat a lot of colors.

Navindra Seeram:

Exactly. And plants are fundamentally, they're going to be... They're going to be variable. They're variable. A green tea from India is going to be different from green tea maybe of the same species or sub variety, or whatever it is from California. So, how are you going to ensure that you're getting that perfect quantity, or that number of polyphenols, whatever you're aiming for, consistently in a standardized form from foods. That's one of the pluses of supplements. However, you have to be cautious in that the supplement that you're getting is a good supplement. How do you know that too? So, that's another question to ask.

Dave Asprey:

Yeah, there's quality issues all over, especially from smaller companies. You need to get really good stuff from smaller companies, or really bad stuff imported from God knows where with no quality control, and it's hard to tell unless you're an experienced buyer.

Navindra Seeram:

Exactly.

Dave Asprey:

So, I'm 100% with you there. All right. I want to dig in then on Urolithin A because I've been a fan of pomegranate for a long time. When I lived in California, I had a pomegranate tree in the backyard. They're stupidly full of sugar. But I always thought they were good because they have something called

the palm one enzyme, which is good for detoxing certain pesticides. I had a family member who was crop tested once and got really sick afterwards. And he actually used palm one as part of his detox pathways. But I didn't know much about Urolithin A. So, can you walk me through what it is and what you've discovered about it?

Navindra Seeram:

Maybe I'll start it, and push it over to Chris.

Dave Asprey:

Okay.

Navindra Seeram:

Very quickly. As I said earlier, if your readers are now joining or anything like that, but I had moved to the USA. I had done my postdoc at Michigan, and then I went to UCLA where this is more than 15 years ago. At that time, at the UCLA Center for Human Nutrition I was working with a very famous scientist. His name is David Heber. He's written several books. One of them is *What Color Is Your Diet?* As you just referred to Dave, eating a colorful diet. At that time, we were trying to understand what into pomegranate fruit and juice are bioactive and are going to be important for certain potential health effects that people have observed for pomegranates in animal studies, and a limited number of human clinical studies at that time.

Navindra Seeram:

That if you look at a pomegranate fruit, it has a very thick, leathery rind or a husk, or it's peel. That the pomegranate is really regarded as the king of fruits. It has a crown on its head at the top. And it's an all of the holy books. It's an interesting fruit where the rind is not edible. You've got to really have to love bitter stuff.

Dave Asprey:

It's bitter.

Navindra Seeram:

It's very bitter. Although in Indian traditional system of medicine known as [inaudible 00:15:46]. They would take a rind, and they would make a spice of it. And in certain cultures like in Iran, and Persia, they will take the pomegranate and really soften it up before they stick a straw and drink the juice. So, where I'm getting, where I'm going with this is the seeds which are the covered with these beautiful red fleshy. It's called the Aril, the A-R-I-L. Those are the edible parts, and the red ruby color, those are because of certain polyphenols known as anthocyanins, which are responsible for giving separate berries, and certain other vegetables, and grains beautiful color.

Navindra Seeram:

But it turns out that in the peel of the fruit, there's this large class of polyphenols, which Dave you know about polyphenols very well. Polyphenols are probably the most abundant and ubiquitous phytonutrients, and they use that word phytonutrients in our diets in terms of edible fruits and vegetables and grains. And in the pomegranate the class of polyphenols which are most abundant are known as ellagitannins. And in particular, there's an ellagitannin known as punicalagin named after the

botanical name or the Latin name of pomegranate, which is *Punica Granada*. So punicalagin as well as other ellagitannins are known as hydrolyzable tannins. It means that without getting into too much chemistry, when you consume these polyphenols and it gets into the body, they hydrolyze in the stomach because of its acidic pH, as I mentioned earlier, it's acidity, and they release ellagic acid into circulation.

Navindra Seeram:

So, the enigma that we had at that time when we were studying the consumption of pomegranate food products, punicalagin, it doesn't survive in the stomach, nor ellagic acid in very, very tiny quantities in blood, so what the heck is going on? And it took us some time, and our group at that time as well as other groups, for example, in Spain, got to the understanding that the ellagitannins and ellagic acid as they get into the guts in the lower colon and the colon, that they were subjected to biotransformation by gut microflora to convert them from their ellagic acid form into these class of [finolex 00:18:39] called urolithins of which Urolithin is one of the most abundant. So, it turns out, and I'm sure Chris is going to jump in here in a little bit, that the conversion of ellagic acid to urolithin, and Urolithin A, urolithins, which would then enter, the urolithins enter a hepatic circulation, and then those molecules would achieve physiological level.

Navindra Seeram:

So, if I were to jump, make a leap of faith, that to get the potential health benefits of pomegranate, you would need to produce your urolithins in the body because it's not the natural compound. However, this is where the catch is. Your gut microflora, Dave, and Chris's, and mine are quite different. We have this natural inter individual variability that happens between, I don't know, ethnicity, maybe the foods we're used to eating, and therefore, I may be a converter, or a responder, or someone who is able to produce because of my microflora urolithins from ellagic acid, but you are not.

Dave Asprey:

You are one of the most highly cited scientists in agricultural science for five years running. And you've partnered with Chris to launch Mitopure. You're supporting Chris with Mitopure. And Chris, you've got a degree in cell and molecular biology. And you've spent 20 years as we talked about before figuring out okay, how do we take these compounds? And how do we bring them to market so people can take advantage? And you guys partnered around this idea of Urolithin A, which you can't get in pomegranate, but you might get if you ate a lot of pomegranate, if you have the right gut bacteria, and isolated this compound. Tell me more about Urolithin A, and what you have discovered about what it does in the body.

Chris Rinsch:

Sure, Dave. Thanks for asking. So, when we started, Amazentis at the very beginning here in Switzerland, the company was reaching out to try and understand what... Much like Navindra was saying and sharing earlier, what actually are in some of these foods that we're eating and that we're bringing these health benefits to everybody. And so, we were looking at pomegranates, and I knew that Navindra was looking at pomegranate, so Navindra got involved as a scientific advisor early on, and we started looking at what type of compounds might be emerging from the pomegranate and Urolithin A is one of those. And so, we started going into more of the biology of these compounds, the biology of Urolithin A. So, we actually produce Urolithin A. As you know, it's not in the actual pomegranate itself. It is only generated if you have the right gut microflora.

Chris Rinsch:

So, we produce Urolithin A in a very pure manner, and started testing that in the laboratory. We started testing that on cells to see, well, how is this really acting? Is there some type of beneficial action of Urolithin A. And in fact, what we saw was that it was acting on at the level of the mitochondria in cells that we were testing on, and more particularly on muscle cells. We found it very interesting. It was very potent in terms of stimulating the mitochondria. We started testing this on these small worms the C Elegans. Very small worms, and scientists are using those to assess the lifespan because they have very short life, and if you increase their lifespan, you can see that in a very short period of time because they don't live very long. And so, what we saw was that when we started incubating and feeding these worms with Urolithin A, they were increasing their lifespan by about 50%.

Dave Asprey:

I didn't get that one in my Super Human book. I list a whole bunch of different compounds that are going for about 15%, up to 95%. That's one, I didn't know about that study. So okay, guys, you think you're not going to live to 100 and something? If that works on you to the same percentage, well, there's... At least it's possible. All right, keep going.

Chris Rinsch:

Well, so this is worms. Of course, this is not animals or humans, but what's exciting there is that we could see that it was having an effect not only in mitochondria, but it was also having an effect on quality of life at this very simple organism level. We moved on from worms into mice. And we started feeding Urolithin A to mice in their normal diet. And what we saw was that they started... When we were testing just their ability to run, we saw that they started running about 40% further and longer than mice that weren't taking diets with Urolithin A. So, it was a big surprise to us when we saw this. And instantly recognized that there was some type of an effect on the muscle function and muscle endurance from that. We also were looking at muscle strength, and we saw about a 10% increase in muscle strength in these mice. And so-

Dave Asprey:

Over what time?

Chris Rinsch:

Now, at this point we were looking at mice that were metabolically challenged too. They were taking a high fat diet over several months. And so, we thought, "Well, okay, this is something that takes place over several months. You may need to feed and consume over several months. But then we said, "Well, let's accelerate this. Let's actually trial over a much shorter period." And so, we went into older mice that normally have a decrease in muscle function, if you will, just like humans as you get older, your muscle function starts to decrease.

Chris Rinsch:

After we had looked at mice that were taking Urolithin A for several months, and seeing that it was improving their benefits, and in terms of their muscle function, and muscle, let's say ability to run, we looked at older animals. And what we did see there was that at a shorter period of time of consuming, we were able to induce an increase and endurance of about 40%, as well. So we thought this is very exciting, of course, and this encouraged us to take this to the next level, and to bring it into humans. And

so, that involved a whole other step of basically taking Urolithin A and making this at a purity and a quality level that was fit for human consumption.

Chris Rinsch:

The first study that we did in humans was a single ascending dose and a multiple ascending dose study with Urolithin A. And we did that, the multiple ascending dose, we studied the effects over a month. And what we saw was an impact directly on the mitochondrial function in the skeletal muscle tissue. So essentially, people were taking soft gels that contained Urolithin A on a daily basis for a period of a month.

Chris Rinsch:

We looked at two types of biomarkers. One biomarker by taking a muscle biopsy at the very beginning before starting to take the product, and at the end after a month. And we looked at the gene expression profile. And what we saw was an increase in mitochondrial gene expression. So very exciting to see that the effects that we were seeing in cells at a cellular level in the lab, and in the worms, and these, and then in mice were actually translating into humans, and we were seeing this type of beneficial effect on the muscle cells.

Dave Asprey:

And as I understand it from looking at the literature before the interview, it's primarily because of mitophagy. Is that the only or the main effect, or there are other things going on, and can you tell people mitophagy is?

Chris Rinsch:

Yeah, it's an excellent point, Dave. So, Urolithin A is acting on the mitochondria and improving the mitochondrial function by stimulating a pathway that's called mitophagy. So what happens is as you're getting older, and you're leading perhaps a more sedentary lifestyle, the mitochondria that are inside of your cell, they start to get damaged and they get old as well. And so, each of our cells that are containing mitochondria, they have an innate process of cleaning up the damaged mitochondria and recycling them, and this process is called mitophagy. And so, as you get older, mitophagy declines. And so, the number of healthy mitochondria inside of your cell declines. And so, your cells are less, let's say bio energetically optimal, if you will, with that decline. So, consequently, the cells aren't functioning well.

Chris Rinsch:

Mitochondria are a little bit like batteries inside of our cells, so they get run down. And so, what we've seen with Urolithin A, and this was a subject of a paper that we published several years back with Professor Johan Auwerx who works here at the EPFL in the journal Nature Medicine was that Urolithin A was stimulating or is stimulating mitophagy and inducing this recycling process of the damaged mitochondria to keep your cells and your mitochondria very fit, and very bio energetically, let's say optimal, if you will.

Dave Asprey:

There's plenty of evidence around Urolithin A for me to have started taking it. I think it's too early for me to say I felt a huge difference. I do a lot of mitochondrial stimulation, and mitophagy stimulation, but

this is something that I'm permanently adding based on the evidence to my personal stack. And you guys put it in Timeline.

Chris Rinsch:

Yes. Timeline, we've put it into this product here. It's a little sachet that you can basically pour into your smoothies in the morning, into your yogurts, and into your cereal.

Dave Asprey:

Is it heat stable?

Chris Rinsch:

Well, we have seen, yes, that it is heat stable, yeah.

Dave Asprey:

I haven't tried this yet because I don't want to ruin it. But if I put it in Bulletproof Coffee, and I blend the crap out of it, am I going to break it up like you would with peptides or is it going to be stable?

Chris Rinsch:

No, I would say you should be pretty comfortable blending it in your coffee.

Dave Asprey:

All right. I'm going to give this a shot. I think it'll add a little fruity note, and I don't think it'll be bad. And I have put grape seed extract in coffee because it is kind of like a dried tannin note, like a dry wine, depending on which brand of grape seed extract. So this isn't the tannin anymore, but I'm going to give that a try. I should have done it before the show. I just don't want to waste a perfect good sachet of Urolithin A if I was going to deactivate it or something. Okay. Why can't I just take a Urolithin A capsule? Why do I need a powder?

Chris Rinsch:

Well, we started out with this powder because we thought it would be a great consumer experience. So many people are used to taking pills all the time. But what we see is this nutrition of the future is going to be nutrition that is studied scientifically and clinically proven to have a benefit that's targeted for you. And so, we wanted to introduce our product in a powder form that you could include into your food. Now, some people like to eat things in food. Some people like to take pills.

Dave Asprey:

I'm rooting for the pills because I already take a handful of pills. It would be easy to toss one in. But in the meantime, I'm really intrigued at the idea of stacking things that add autophagy or mitophagy. And so, the idea of what if I did Spermidine and I did Timeline together during a fast, and then exercising at the end of the fast, and things like that. Of course, there aren't studies about this stuff yet. A lot of people saying, "How do I get more out of an activity that I'm already doing?" And so, I'm already in my mind going, "All right. What's my timing going to look like for this?" And it seems like, either during or at the end of a fast is when I'm going to start using Timeline because that'll probably more convenient anyway.

Chris Rinsch:

Yeah, I was going to say in terms of how you use it in the actual effects, we were speaking about one of our earlier clinical studies. But more recently, we've done a clinical study that was four months long where people were taking a Timeline on a daily basis over a period of four months at 500 milligrams. And what we saw was an improvement in leg muscle strength after that four month period. We also did similar types of tests that we did in our initial study where we looked at biomarkers, not only in the muscle, but also in the plasma. And we saw an impact there, particularly on a Acetyl Carnitines, decrease in Acetyl Carnitines over time showing an impact on mitochondrial function.

Chris Rinsch:

Basically, as Acetyl Carnitine levels are higher, that's indicative of mitochondria that are less healthy. And so, as they go down lower, that's a sign that your mitochondria function is improving. And the fact that you see that in your plasma is an indication that there's something happening not only at the level of muscle that we saw when we did these biopsies in the leg, but also more systemically in the body. Of course, all of our cells except for our red blood cells contain mitochondria. But so far the focus of our research has been on the skeletal muscle, and on your muscle function and strength. And so, I see in the future, a possibility to examine other potential beneficial effects of Timeline in other areas of health.

Dave Asprey:

So, that study that you referenced was on people aged 40 to 65 years, which is kind of cool because the research that was backing a lot of what I did with Superhuman, and even a lot of what I'm doing the Fastest Way, it says everyone over age 40 has early onset mitochondrial dysfunction. That's Frank Shallenberger's research, which is based on measuring oxygen consumption efficiency. So, it's very clean. We don't know exactly what's going on. But we know what goes in and what comes out. So we can tell they're not working the way they used to. So you targeted the group where everyone has an issue, which is pretty neat. And then you found that they got stronger leg muscles after four months of taking it on a daily basis 500 milligrams. What's the dose that's in Timeline? Is that the same dose?

Chris Rinsch:

Yes. We've included 500 milligrams in our daily dose. And in each of these little sachets. And so, yeah, so this is this gives you a very convenient way of getting the product. Now, if you say, "Well, okay, I'd prefer to get it through," and you were referring to natural ways, and so was Navindra, through a pomegranate. Well, you'd have to have a lot more pomegranate juice a day. In fact, what we've recently, this year completed a clinical study where we did a head to head comparison with one glass of pomegranate juice, and one sachet of Timeline mixed into a yogurt. And we looked at the bioavailability of Urolithin A in the blood during the first 24 hours after taking it at several time points and blood draws. And what we saw was that there was about a sixfold higher level of Urolithin A looking at this area under the curve for that first 24 hours when you take one sachet of Timeline versus one eight ounce glass of pomegranate juice.

Chris Rinsch:

And this is also... And the another thing that we found was that those people taking pomegranate juice, we only saw about 40% of people who are actually converting, and this was sort of you had low converters, and mid converters, and high converters, where all the rest weren't able to do that conversion. So, which really highlights the value of one, you don't want to be taking six glasses of pomegranate juice every day. And if you can take one little sachet that contains 500 milligrams of

Urolithin A, you're getting a really precise dose that's been scientifically and clinically evaluated in humans to give you a physiological benefit. And so, we're really excited to be able to do that and offer this to people in a convenient manner.

Dave Asprey:

One of the problems with pomegranate juice is like any fruit juice, if you take one eight ounce glass of that stuff, and you're doing continuous glucose monitoring. I use the Levels Health device to do that, you're going to have this postprandial blood sugar spike that is ageing, and that it causes advanced glycation end products in the body. So, I couldn't in good conscience tell people listening, "Hey, drink a big glass of sugar water with some ellagic acid in it on a daily basis." Because the long term effects of any kind of fruit juice are not that good on the human body. What is the likelihood of any change in blood sugar from Timeline? Have you guys looked at that at all?

Chris Rinsch:

Yes. Well, in terms of our product, we haven't really seen any type of negative or side effect of our product. And we've now studied it in many people. And that one juice study that I refer to over 100 people took the product.

Dave Asprey:

They didn't see big blood sugar swings.

Chris Rinsch:

Very low level of sugar. Were around two grams of sugar in a sachet here.

Dave Asprey:

Almost like no change for most people on two grams is almost invisible. So that's... In my mind, if all you did was take the sugar out of pomegranate, and made a supplement from that, like you're saying, "Well, only 40% of people could convert, and they would convert at one sixth of the dose." And so, now what we're getting is much, much more than you could conceivably drink during the day and you're not getting the harmful sugar and whatever else is in there. Usually preservatives are present in it as well.

Dave Asprey:

Is it advisable for people to continue supplementing Carnitines or at least eating lots of red meat when you're using Urolithin A. Again, you don't have a study here, but we understand the mechanics of it. Do you guys have some thoughts on that? I know this is not clinically studied. This isn't... What do you think?

Chris Rinsch:

I think what, there's a number of other supplements that are, I would say fuel for the mitochondria and ensure L-Carnitine. It could be a good supplement, and it's known as something that you can take fuel your mitochondria, so to speak. The big difference between an L-Carnitine and other supplements that are acting in that similar fuel like manner, and Urolithin A. Urolithin A is really optimizing the actual function of your mitochondria where the L-Carnitine is more helping the processing, and the functioning in general of the mitochondria. So, together, they could most likely be beneficial, I would say.

Dave Asprey:

Okay. So, there's no reason not to keep taking your Carnitine, whether it's acidulated or not. Okay, that's good to know. And for a lot of people who are listening, I'd say the average dose is about 500 milligrams. I took it for a long time. I don't take Acetyl-L-Carnitine now because when I do it raises my acetylcholine levels too much. I actually get jaw tension from it because my mitochondria are working just fine. But I have no issues with the Timeline that I've had so far because it doesn't change your Carnitine levels, as I understand, and it's unlikely to change acetylcholine levels, I would guess. Given what you guys know about pathways, are my acetylcholine levels good? By the way, most people want more acetylcholine. I just already have enough. Anything going on there that you've considered?

Chris Rinsch:

We haven't really been studying the effects of Urolithin A on acetylcholine.

Dave Asprey:

Okay. There are studies out there that showed that the size and strength of your quadriceps, your leg muscles are correlated with the number of synaptic connections in the brain, and with cognitive function. This is why you do squats. And if you have a nice butt, you probably have a smarter brain to be perfectly honest. We know that independent of Urolithin A. These are just we know, the brain likes to know, I guess I should get bigger if I have more muscles to deal with. And the mechanism for that isn't clear. So, I believe very fundamentally that you got to get your mitochondria in order. And there's many different ways to do it. And this seems like a new and interesting way. Now, here's where I'm going with this. 52% of... or sorry, 48% of people under age 40 have early onset mitochondrial dysfunction, according to John Berger's work. Now, if you were, say, 25, and you were not one of the people who had early onset mitochondrial dysfunction like I did, are you likely to see an improvement anyway? Or is this mostly for people whose mitochondria already kind of going off the rails?

Chris Rinsch:

No, I would say that if you're... It's really important to keep your mitochondria at its peak performance, no matter what your general health conditions are. If you take... And we've seen this in preclinical evaluation. We've seen in younger animals. We've seen the animals who are taking Urolithin A improve their running, as well as in older animals. So, this is not something only for people older than 40. It is not something for people only older than 60 years.

Dave Asprey:

It works throughout the entire lifespan. Okay.

Chris Rinsch:

Yeah.

Dave Asprey:

My advice for listeners would be, it's a lot easier to stay young than it is to get old and then make yourself young again because I've done the second one. It's damned expensive, and it takes a lot of time and energy. And I know people who start younger, and they just spend less money and spend less time and they enjoy their life more. I was hoping you were going to say that it was still effective for younger

people. But since you've seen changes in muscle strength, are there pro-athletes who are incorporating Timeline into what they do? Are you guys NSF listed, and all of that?

Chris Rinsch:

Well, that's a great point, Dave. Look, we think that Timeline would be great for people performing various sporting activities, and that could be pro-athletes. We're in the process of getting the NSF certification, and we'll have that this next year.

Dave Asprey:

I've got a couple friends who are very, very high up in their field of sport, and I'll reach out to them privately and a lot of them are saying, "Well, it doesn't have to necessarily say NSF as long as it doesn't have banned compounds in it because NSF is very expensive." This is, for people listening. It's a certification that supplement companies can go through that assures that an athlete who takes it will be okay. Many pro athletes though, they're clearly not violating any rules, but they're saying, "Well, as long as I know what's in there is what's actually in there. I'm okay." What they don't want to do is take some cheap, weird thing, they bought off a random website, and then it has stuff that wasn't on the label then they get in trouble. So, I see a great degree of variants depending on which athlete it is. But it seems like you might see some changes from strength athletes. What about endurance? Is it going to make a difference for those weird people who still like to run marathons as if something's chasing them?

Chris Rinsch:

Well, I would hope that it would increase endurance by acting on your muscle cells and your mitochondria.

Dave Asprey:

It should, right?

Chris Rinsch:

It should improve general muscle function. Back to your point on this question of questionability of actives and ingredients that are sold out there. I think one of the things that it's important to note is that with our Urolithin A ingredient Mitopure that's in Timeline, we've actually gone through the whole FDA grass process. So, our product is... It is very, very pure. And so, there's no issues of any type of banned substance as well.

Dave Asprey:

Are people going to see an immediate energy boost from this if they have mitochondrial problems?

Chris Rinsch:

Well, what we've seen, as I was saying earlier, each user has experienced effects differently. So some users say, "Well, I'm seeing an effect right away. The first day I take it I feel an increase in let's say your muscle function or endurance. Although, I would say that this might be a little bit optimistic to see something instantly-

Dave Asprey:

Placebo's real. I mean, big pharma uses placebo all the time. Just beat it by a few percent, and there you go. So, some of it could be placebo, but you have long term clinical studies. And when I see it in worms, and in mice, and in humans, it's probably not placebo because mice aren't really that susceptible to it.

Chris Rinsch:

Right. And when you study something, we ran ours, our clinical studies are double blind placebo controlled studies. This is the same quality that pharmaceutical companies use when they evaluate drugs. And so, what we saw as I was mentioning earlier in most recent studies is that we improve muscle strength after four months. And so, this is a real effective that takes into account a placebo effect. And no, we're very excited about this. We'll be running more studies. And I think, yeah, and now, one of the interesting avenues forward will be the additional new clinical studies that we will be running. And we're doing this together with one of our partners. Last year, we partnered up with Nestle Health Science, which is one of the leaders globally in nutrition. And so, we are conducting new studies together to analyze different pathways and different mechanisms of actions and benefits that we can bring people.

Dave Asprey:

That's fantastic. I love it that you're continuing to study this a lot more than some compounds get because it's a metabolite, and because it's the only way you can get it, and the way we would do it before, you have explained very, very convincingly for me why I didn't see the benefits when I did take ellagic acid because I'm one of the 60% of people who doesn't do anything that make us have to pee. So, that was really enlightening. I'm really excited that I can take Timeline. And this is something that I'm on the one year subscription plan. So, I will be continuing to take it for at least a year and measure my results and see how I'm doing.

Dave Asprey:

I also appreciate that you guys are offering a discount for people listening to the show. [Timelinenutrition.com/DAVE](https://www.timelinenutrition.com/DAVE) and you can get 10% off if you use code Dave 10. And you guys do four, eight, and 12 months subscriptions because you've seen results for sure after four months in your studies, which is kind of cool. So, you're like, "Look, you can't just do it for a month. Do it for four months so you know."

Dave Asprey:

Can I do two at a time?

Chris Rinsch:

Yeah, I've done it two at a time. Yeah.

Dave Asprey:

Okay. I might just double up. I'm a big guy.

Chris Rinsch:

Yeah, we've had people that say, "Hey, I've been taking it once. And now I'm doubling it up, and I'm feeling better. I did that just the other day. So-

Dave Asprey:

I'll do that.

Chris Rinsch:

We've been studying the pomegranate in Urolithin A now for over 10 years. And I think one of the most surprising things that we uncovered was that this metabolite Urolithin A was acting on mitochondria because when we started looking at the pomegranate, we thought there could be a whole host of different bioactives that were responsible for the pomegranate's benefits, health benefits that were being spoken about. And when we started really diving into the pomegranate, and studying it, and looking at this metabolite, we were very surprised to see that it was having such a potent effect on mitochondria. I think that this thought that it can translate this effect from a cell into this miniature organism, the *C. elegans*, and extend its life lifespan by about 50%. This was already something quite surprising because there's not many [inaudible 00:53:54] that can extend the lifespan of a worm by so much.

Dave Asprey:

It's more than caloric restriction, by the way.

Chris Rinsch:

No, much more. And you see that you're boosting this mitochondrial function. When you look at these worms, as they get older, they're more active. And when we went into mice, and we were feeding old mice a regiment of Urolithin A in their foods, and we saw this improvement in running endurance where we really, this was really an observation that we had that surprised us because we thought, "Well, maybe you need to take this for six months to see... For mice to take this for six months to see an effect." But we saw in a very short period of time. And the fact that it translated to humans. There's not many products that are translating from cells, to mice, to humans, and showing this conservation of a mechanism of action.

Chris Rinsch:

And the fact that we've been taking as a population, around the world, pomegranates and consuming all of these fruits and nuts that contain the punic elegans, and ellagitannins that are the precursors of Urolithin A. One, you can feel very comfortable about the safety also of the product. So, I think this whole, the whole story about how we consume the foods, and we extract this Urolithin A, and that it basically powers the batteries inside of ourselves is something rather amazing. It's a lot different than what we've been told in the past that what's inside of your food is if you eat the right fruits and vegetables you'll get all of the right nutrients that you need. But in fact you need to have a mixture of the right foods, but also having that right gut microflora to be able to extract those, the benefits from these compounds that are found in the foods we're eating.

Dave Asprey:

I'm with you on the 50% increase, just having reviewed so much literature on all the different things that increase lifespan in worms, and probably in other higher life forms. And caloric restriction has been the gold standard, and seeing a 50% increase, this is probably the second or third most effective that I've come across in research. And yes, it doesn't translate direct to humans from worms, but directionally, it's probably going to give you a bump. And from my perspective, we all want to be able to do that. And we all want to be able to find the right combination for us that can do it. And you've contributed

something after 10 years of research, something new to the world of supplementation for anti-aging and muscle function and mitochondrial functional, all that, which is really cool.

Dave Asprey:

And so, thank you for being on the show, Chris and Navindra. Your curiosity and willingness to go to places that haven't been done before to do real clinical trials. And to make a product that looks like it's got lots of evidence behind it, that it could do all sorts of good things for the body because from where I sit, mitochondria are the thing. You get those working, and they'll fix a lot of other stuff. And if they're not working very well, they won't fix a lot of other stuff. So like I said, Timeline is now an official part of what I'm doing. And I'm constantly evolving what I take. And I'm going to be doing this for at least the next year. And I'm probably going to double up on my dose just because like I said, I'm a big guy. And because, hey, if it works, maybe you just take more. Kidding, that's bad advice, but in this case I'll do it. And so, I want to say thanks for your research.

Chris Rinsch:

Well, thank you very much for having us, Dave. Enjoyed it.

Navindra Seeram:

Yeah, thanks, Dave.

Dave Asprey:

Now guys, timelinenutrition.com/DAVE. Use code Dave 10 and save 10%. And if this is within your means, you just heard all the evidence. These guys know what they're talking about. These are very well credentialed guys who've done something that no one else has ever done before that's right in the alley of biohacking, and I think you should give it a try. I definitely have. Have an awesome day.