



## **Episode 227: The Amazing Anti-Aging Benefits of Resveratrol**

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David Roberts:

Hey everybody, it's David Roberts and you're listening to the Mara Labs Podcast. And today I've Dr. John Gildea and Dr. Martin Katz with me. Hello gentlemen.

Dr. Martin Katz:

Good afternoon.

Dr. John Gildea:

Hello.

David Roberts:

And we will be talking about a topic we have not covered before. It's called resveratrol. Resveratrol is a plant-based nutrient, a phytonutrient that is most commonly thought of as being in red wine and has been thought to be responsible for what we know as the French paradox where French people eat fatty foods and yet have decent heart health, but because they drink lots of red wine. And so we will be talking about French paradox, but also really digging into what pathways resveratrol impacts, why it is good for anti-aging. And, so thanks again guys for joining me and let's just dive in.

Dr. John Gildea:

Where should we start do you think? Just of a little bit of a history, where it became popular? I think the longevity studies are at least when I started becoming aware of resveratrol where they did studies in *Caenorhabditis elegans* and fruit flies and yeast. And then pretty soon after that found the connection to SIRT1 and those were the initial experiments.

David Roberts:

So talk to me about SIRT1, because that's an important.

Dr. John Gildea:

SIRT1 is a classic pathway that is induced by fasting and is also involved in insulin signaling. And so in the *Caenorhabditis elegans* studies, the original studies were they found a mutation in the insulin receptor and these small model genetic organism lived upwards of double its lifespan. So a really dramatic changes. And then they started doing genetic screens to find the pathways. It was very clear it was insulin signaling.

Dr. Martin Katz:

Was there some deacetylase as well in those small creatures?

Dr. John Gildea:

Yes, SIRT1 actually is a histone deacetylase, so that is the part of that pathway. They have all the genetics in *Caenorhabditis elegans* worked out pretty well. But that is the sort of connection to insulin and longevity that people have been chasing down for a while.

David Roberts:

And I know we just recently covered, histone deacetylase in another podcast. However, assuming people have not listened to that one, can you dive in on what that is and why it's significant?

Dr. John Gildea:

Yeah, so the 20,000-foot look at that is people may not know that DNA is wrapped up in very tightly wound complexes so that you can get the basically three meters of DNA wrapped down into somewhere around eight micron nucleus. So it's massively compacted. And so as you compact that DNA down, the places where you want access to transcription factors to turn on genes are generally considered to be open chromatin or euchromatin. And the places where they're packaged away and inaccessible would be heterochromatin. And so one of the ways that they're packed and unpacked is through histones. Histones are the actual protein that DNA is wrapped around and whether they're accelerated or not, makes them unwind and makes them accessible for transcription factors to turn genes on and off.

Dr. Martin Katz:

Well said.

David Roberts:

Well said. Yeah. And so SIRT1 is histone deacetylase, and how does that tie into health benefits?

Dr. John Gildea:

Yeah, so at least the background of that is there a lot of research in between those initial studies and all the follow-up. But I think it can be basically summarized as saying what is aging? Aging is DNA damage that distracts your chromatin regulating genes from remembering who you are. So if you had to put it all into a little package, it is that when you get a double stranded break in your DNA, it distracts a bunch of these molecules that make that cell remember who it is. So basically it's loss of information and there's tons of places we can go from there. But basically a SIRT is involved in that pathway because SIRT is both involved in DNA repair and in remembering the on or off state of genes.

David Roberts:

So I mean, we're there. Let's talk about resveratrol and antiaging.

Dr. Martin Katz:

Yeah, I mean this would be a topic for, I would say the entire population. Everybody would be interested now in healthy aging. Hopefully you are, as I've often said, everybody in my clinic when I ask them if they want to be healthy, fortunately nobody says no. So obviously you want to age well and that would absolutely include awakening in the morning, feeling healthy. So when you look at this compound resveratrol and the effects it has on the cells, specifically as we're talking about sirtuin has been shown to be resveratrol's effect. And so when you ingest foods, you would hope that resveratrol would turn these molecules on.

The problem that we're seeing with resveratrol it does seem to be dose dependent. So whether you're looking at sirtuins or you're looking at its effect on insulin or other effects that this fantastic molecule has, you have to get it to the cell in a dose dependent manner. And eating foods that are high in this does not necessarily do it. And that's why we're so interested in this molecule to try and affect its bioavailability and therefore its effect on healthy aging and its effect on sirtuins.

David Roberts:

And so Martin, do you suggest people in your clinic take resveratrol or who? And if so, who?

Dr. Martin Katz:

Yeah, it's a great question. I would say at this point I'm still looking for a dose dependency and I think the studies are not quite there yet. I think we are going to be looking at that and trying to figure it out. And I'm not sure John could probably speak more to how many human studies there are and the dosing in sirtuins. At this point most of the studies have been done on rats and small worms and other types of creatures that are obviously not human.

And so we need to figure out how that's going to work in humans. I do absolutely think resveratrol has effects that have been shown to be effective with blood pressure and insulin resistance and possibly what's called GLP-1 agonist. So we can talk about that and it's effect on sirtuins with David Sinclair's work have been shown to be quite effective. So I do recommend. Resveratrol's probably not one of my first molecules to recommend for folks, but it is up there.

David Roberts:

And so John, you take resveratrol, don't you?

Dr. John Gildea:

I do, but from the human studies it's pretty clear that the dose that's normally recommended over the counter is not adequate. Like Martin was saying, it's very dose dependent. So the studies have gone from in between a 100 milligrams to 5,000 milligrams. And for most of the studies they've done in humans, there's a clear dose dependency to it. And so obviously 5,000 milligrams of resveratrol will be outside of the range of most normal people in dosing just for price. Because this particular molecule is on the higher end of the price index per milligram. And so I think maybe some of the best examples of that are the effects on blood lipids. And so those are pretty easy to study in humans, just they're already measuring your blood lipids and so they've seen this dose dependent effect on positive effects on blood lipids. So I think that's the clearest human data that's out there.

Dr. Martin Katz:

And I'd say clinically, the way I use it, again, we have so much, we love to talk about synergy. And so in somebody who's really struggling, I have so many people come to my office and I do love to talk about this, health is on one side of a scale and on the other side is disease. And the needle has moved over a period of years or decades in some people's lives, gosh forbid they were smoking. But a lot of folks are just not exercising enough, eating enough, quite sedentary, not sleeping, too much stress. And so there's needle over time, moves closer and closer to disease.

And I like to tell people that they have an effect on that needle. What they doing can push that needle back to health. And depending on where that needle is, certainly wouldn't be clear that we love Sulforaphane or love curcumin, certain other supplements, omega-3 S, vitamin D, you don't have to get into all those, but resveratrol has its place. And again, I think it's a synergistic molecule. And if you look at how it works on NF-κB, nitric oxide, insulin resistance, obviously sirtuins, we've talked about that, I think it has its place. And so I will then suggest to somebody that this is a molecule that deserves to be in their repertoire.

David Roberts:

Now I know David Sinclair takes a gram a day, and so how much do you take John, a day?

Dr. John Gildea:

Yeah, so-

Dr. Martin Katz:

Outside of the red wine, John.

Dr. John Gildea:

Yeah. I was going to say the supplements that are cost effective seemed to be 50%, resveratrol in a matrix extracted, so a 50% extraction. And so our current dose is 1,500 of that extract. So me and my wife both take that and probably, it's a good time to bring up the fact that it induces NAD, but you can push on both those pathways by taking NMN and resveratrol at the same time. So I think that's an important consideration there that we take both of those, take NMN and resveratrol at the same time. Those two feed into the same pathway.

David Roberts:

And so talk more about that because some people may not know NAD, some people might not know NMN, and I'm blanking on the, I don't even want to try to pronounce what NMN is, but yeah, go talk about more about the NAD.

Dr. John Gildea:

Nicotinamide mono nucleotide. The pathway is energy metabolism, which is pretty clear that everything that has to do with epigenetics is tied with energy metabolism. At least in my mind, that's the connection there. And there are a lot of connections to mitochondrial function and NAD production and nutrient sensing. So probably the pathway when we're talking about NMN, at least the clearest for me is its mitochondrial effects. And resveratrol is probably one of a handful of molecules that activate a mitochondrial transcription factor called PGC-1 alpha. And so when resveratrol activates PGC-1 alpha, you are basically stimulating the pathway that is most famously associated with exercise, back to Martin. So-

Dr. Martin Katz:

I was about to say something, John. Thank you.

Dr. John Gildea:

So that's the connection. And so when we talk about energy metabolism, exercise just comes up very clearly and exercise improves mitochondrial function. And then if you can improve mitochondrial function, that willingness and ability to go out and exercise, they feed off each other. You're more likely to get up off your duff and exercise. And that's the connection. And it always rings in our head when you talk about mitochondria and exercise. So Martin is very good at reminding us that you probably shouldn't take a big regimen of supplements until you start moving a little bit, but it's really both, not an and or.

Dr. Martin Katz:

Yeah, it's interesting. I was recently listening to Peter Attia on aging at a fairly extensive podcast, and I think he threw out there, if you can't do 15 pull-ups, I think it was, which is a lot, I thought it was a little over the top, I would be more like five. I can do more, but I think what the important message there

where he said, if you can't do 15 pull-ups, you should not be able to argue whether you should be carnivore or vegan. If you're arguing nutrition, you need to be able to do some serious pull-ups.

Point being, as you just pointed out, the benefits of a lot of these molecules are better with that hormetic stress of exercise. So again, to remind people what hormetic stress, again, not all stresses are bad. Stresses can be very, very, very useful. When you're challenging a cell that may or may not be doing so well, if you challenge that cell to be better and then give it the molecules to support that improved health, whether it's autophagy, again, cellular protein changes in to make him better or mitophagy improving that mitochondrial health, that is just so incredibly important.

And that's again, what exercise provides to the body is that hormetic stress. And then as an individual, you providing those molecules that are absolutely needed to build that base is important for sure. And sounds like we're giving resveratrol the thumbs up for sure.

Dr. John Gildea:

Especially if you can get it in even just a little bit higher doses. It seems like for those studies, and you were talking about NO and endothelial function and-

Dr. Martin Katz:

Nitric oxide.

Dr. John Gildea:

Yeah. Those are pretty clear. Starting to become clearer in human studies too. So it's also a dose there. So within that fivefold dose of just straight resveratrol, you start having much bigger effects. So that's the goal.

Dr. Martin Katz:

Yeah, that was interesting. I was a little sad to see that the foods, and again, foods are such a hard thing to tabulate 'cause a lot of times they're not provided, you're getting people's report on food, but that food's high in resveratrol consumed was not as effective as a supplement again. And that's that dose dependency, much harder to get those higher doses of resveratrol in food rather than a supplement.

Dr. John Gildea:

The grape skin and grape seed seems to be how most people are extracting resveratrol, but it's also in peanut-

Dr. Martin Katz:

Peanuts, pistachios.

David Roberts:

Peanut skins.

Dr. John Gildea:

What's the little skin that's surrounding regular peanuts that in most cases they throw them away. So yeah.

Dr. Martin Katz:

Don't throw away your skins.

Dr. John Gildea:

Yeah, the skin.

Dr. Martin Katz:

Oh, unless you're talking about orange skin.

David Roberts:

So John, so the three fourths of a gram, 750 milligrams of Yeah, the that you take, is that just regular or do you have... So basically let's talk about by availability, because that impacts the dose dependency. How much is getting in? So if you take that 750 milligrams, how much is getting in?

Dr. John Gildea:

So that's a complicated question. It's a metabolism issue. And so maybe it's good to just say what are the issues that are outstanding out there is there are studies, especially of cells, isolated cells where it does seem to go across, for instance, a Caco-2 layer that's a interosse model. So it seems to be able to go across the interosseits almost in a diffusion like state, but it's very insoluble. So you have both of those effects happening at the same time. But in liver and in interosseits, there's some conversion to the sulfate and glucuronidate versions of resveratrol. So it's hard to map all of them. And I think some of the best studies out there are where they look at the total amount that makes it into urine. And so similar to how we're studying curcumin is you measure the total amount of resveratrol that goes into urine.

We're talking low bioavailability, a few percentage points. And a big component of whether it works or not, I think is might be still an outstanding issue, is that it tends to bioaccumulate in cells. So cells seem to have an ability to desulfate with Sulfatasis and so it can accumulate in the cell. So it has a very complex pharmacokinetics and the circulating levels are pretty short also. So I think the strategy for making a more bioavailable one is make it soluble. It's the first step. Two is to try and increase its longevity in the bloodstream so it can make it to the cells that are able to then utilize it. And then you wouldn't be as dependent on the few cell types that are able to desulfate and [inaudible 00:19:40] oscillate because the function of the resveratrol is decreased when it's metabolized. Unlike kerastin where it still functions when it has glucose molecule attached to it, resveratrol is a pretty dramatically decreased function when it's glycosylated or glucuronidated.

Dr. Martin Katz:

So John, that's interesting. So should we be taking it away from sulforaphane then?

Dr. John Gildea:

What's interesting is I think the sulfation and glucuronidation is interesting in that I think some of those phase two molecules could affect resveratrol. I haven't seen studies where so sulforaphane exactly enhances it or inhibits it, but that would be a connection.

Dr. Martin Katz:

Yeah. Well there we go. That's good for... Yeah, I would love to know the answer to that and I'm sure a lot of our folks would too.

David Roberts:

So to recap what I heard you saying to my question, the answer to my question about how much gets in, what's the bioavailability, it's more complex than other plant-based molecules-

Dr. John Gildea:

For sure.

David Roberts:

Because of the cell's ability to take it in quickly, but the thought is 1% to 2% of the resveratrol you take actually gets through the gut barrier.

Dr. John Gildea:

And anything. There's a lot of studies with conjugated versions of resveratrol where they're circulating levels are increased and that does seem to increase their effectiveness. So that's one of the goals, solubility and serum half-life.

David Roberts:

So would you recommend the three-fourths of a gram of resveratrol per day for folks who are interested in trying that or David Sinclair's gram?

Dr. John Gildea:

I do that just because it's in the mid-range for cost effectiveness. And then if you take also NMN, it's pretty expensive. So we take half a gram, so we take 500 milligrams of NMN and then the basically three quarters of a gram of resveratrol and that combination is what we think we can feel the difference.

David Roberts:

And so if, I mean money is an issue for most people, but what would be an ideal? Let's say it wasn't, what would be the ideal amount of resveratrol one you one would be suggested to take per day?

Dr. Martin Katz:

Yeah, I mean I guess it depends on what you're trying to affect. I think from a blood pressure standpoint and those endothelial cells, those are a little bit more accessible to most of us. And so if you're looking at a blood pressure perspective, you might be able to get as low as a quarter of a gram, 250, whereas if you're looking for sirtuins and you're looking for more-

David Roberts:

Longevity.

Dr. Martin Katz:

Longevity, I think you're going to be looking at more. So it really depends on what you're after. I'm seeing folks now in the clinic, 32, even late twenties, but early thirties and certainly through the third decade of life, we were having such a difficult trouble controlling their blood pressure. And so do they have to worry as much about sirtuins at that point, at thirties? I guess you could argue possibly, but maybe not quite as much. And so they could maybe get away with a lower dose. And then our older



folks who are maybe looking to really move that needle back towards health, I would say a higher dose with NMN at that point or some type of NAD supplement.

David Roberts:

So for anti-aging, what would be an ideal amount of resveratrol and grams and NMN?

Dr. John Gildea:

I would probably believe David Sinclair, since he's been in the middle of that since the beginning of time, and I'm pretty sure he takes a gram of each.

David Roberts:

Gram of each.

Dr. Martin Katz:

That's a safe bet. Yeah, I think the human studies are still lacking though, but David Sinclair, thank you.

David Roberts:

So speaking of David Sinclair, there are a number of people who do not believe in the efficacy of resveratrol. Can we talk a little bit about that, because I want to head that off at the pass and get it in front of that, can maybe just touch base on the genesis of that controversy and where you stand as far as that argument that it doesn't work.

Dr. John Gildea:

I think it's the same argument for many supplements is the data in the animal or model organism is really clear and it's harder to go from whatever that dose is where they know they've optimized the efficacy of the dose and time you need to affect a pathway, it's just much harder to do in humans. And so I think the skepticism is during that switch, a switch between animals. So yeast was the clearest data of this absolutely clear. And then when they switched to doing mice and other things that the time component becomes a big effect. So in the mouse studies, they were done with high fat diet where you have accelerated aging. And I think that data in mice was very clear.

And then when you move on to humans, it's really hard to parse out the people where you have a supplement that is not really allowed to affect a disease state. So you're just doing the general population. Whereas a person who is really compromised, I think resveratrol would have the highest likelihood of helping, but those studies aren't really being done. They're just large, randomized trials on normal humans and then some form of blood measurement is taken. And so I think the parts that are missing there is also the reason why supplements don't always have the clearest clinical data is because they're not being done on the very sickest, because that's the world of pharma.

Dr. Martin Katz:

And again, I would add to that, so probably the mixed studies on bioavailability, that there's no clear connection at this point, and so it's easy to poo-poo something from that perspective. Fortunately, resveratrol seems to be fairly well tolerated. And so it's one of those things with food where at this point, unless there's significant harm, I think we can't really wait for the studies and especially as John was saying in those more ill folk that want to take a holistic, integrative approach to addressing their health concerns.

David Roberts:

So those are all very good points. I think part of where I was coming from too is there was a pharmaceutical company trying to replicate resveratrol, you know what I'm talking about, and then David Sinclair sold it, or I think he owned it, sold it, and then it was a bust. You are familiar with this?

Dr. John Gildea:

I remember reading about it, but I don't remember investigating closely to see whether what side I fell on.

David Roberts:

So essentially from my understanding, the company was trying to create a biologic, like a synthetic resveratrol, and then that ended up not working. And so they closed down the company and lost millions, hundreds of millions. However, I think people tie that with, okay, therefore resveratrol doesn't work, which I think there needs to be a bifurcation clear distinction between natural resveratrol which does work in the literature and then this attempt at a synthetic, which did not work.

Dr. Martin Katz:

Again, there's a complete understanding of yes, we are not yeast, yes, we are not mice, we're not rats, we are humans. But if you look at the data, the data is quite clear in those organisms that this molecule certainly works and it works in the same pathways that would be very beneficial in humans. And so there seems to be, again, causation correlation, you got to be careful. But in the human studies that have been done, certainly with blood pressure, certainly with insulin resistance, I don't know sirtuins John, but certainly in those studies there is some benefit. So seems like resveratrol has a clear benefit and has an impact on human health, which is what we're interested in.

David Roberts:

Yeah. Yes. And so this is yet another fat soluble molecule, plant-based molecule that we are bringing to market in a highly bioavailable form. It's not available yet, but it will be soon.

Dr. Martin Katz:

And just to state that, David, the reason for that is that, again, it's not an easy molecule just to put in a capsule. Again, we're looking to improve that bioavailable as we continue to make sure our curcumin molecule is the best that's out there. And so these molecules are incredibly challenging and we don't want to just put something in a capsule and say, "Here, buy it. We want to make sure it's great for us, for our families, for our loved ones, and absolutely for me, for my patients.

Dr. John Gildea:

Yeah, and it follows what we've been talking about in a lot of different other podcasts is that the data in cell lines is absolutely clear that it's doing what it's saying it's doing, affects the pathways that we're talking about. But in those cell lines, it's often in the 20 to 30 micro mo range. And even with the really high doses in vivo, they look more like two micro mo. So you're close, but not quite what you're able to achieve in cell lines. So just a tick up in bioavailability, we'll get that into the range where we think it'll help. And most of the time cell lines also are not this model of bioaccumulation either. So there's no barriers to between when you put resveratrol in a cell and getting into the cell.

Dr. Martin Katz:

I also want to be really clear that drinking red wine is not going to do this. And there's so many negative benefits to red wine and a lot of it certainly at night, the effect it has on sleep and insulin resistance and your liver and fatty liver, red wine is not the way to go about this. For sure. And just to be very, very clear.

Dr. John Gildea:

I also got the other end of that is, okay, well let's just drink grape juice. That actually has a pretty high glycemic index.

Dr. Martin Katz:

Very. So yeah.

Dr. John Gildea:

That's the reason why, if you can get it from your food, we'd prefer it that way. But it seems like in this case, the supplement is better than the normal route from food.

David Roberts:

And so you've made the bioavailable form of resveratrol, you probably have the most experience with it. What have you seen in as far as you've taken it, what have you noticed physiologically?

Dr. John Gildea:

So at least for me, the demarcation line is the effects on blood glucose. So it does take up a while to affect the A1C levels and things when you take it in its raw form. But if you get it more bioavailable, you can see a short term blood glucose reduction. And so that's been the metric for developing the product for me is lowering short term blood glucose.

David Roberts:

And is it similar to what we'd see in berberine or verite?

Dr. John Gildea:

Not quite as strong as berberine, but it's a metric that I can tell that it's getting past and in circulation enough to affect blood glucose.

Dr. Martin Katz:

And different mechanisms from what I would understand of the two molecules, berberine versus resveratrol. So again, we have that synergy, which is nice.

Dr. John Gildea:

And I think it is a different mechanism. There's not a whole lot of overlap between those two.

Dr. Martin Katz:

Yeah.

David Roberts:

Have you looked at synergy between resveratrol and other products that we're -

Dr. John Gildea:

I haven't, but there's hints of that in the literature from us. Again, cell line studies with resveratrol and other molecules for cancer, in vitro models of cancer, that is basically saying resveratrol with something else that is known to kill cancer cells, that it does enhance it. So there's some nice studies there.

David Roberts:

Great. Well, anything else you can share with our audience about the form of resveratrol will be releasing soon?

Dr. John Gildea:

I'm excited to see if people can feel the effects of resveratrol just in your general wellbeing. My wife and I, and a number of people that we've told to take the higher doses of the regular resveratrol with NMN have been able to tell just a general feeling of wellbeing. And then in this case, getting a slightly higher dose of resveratrol and its effects on mitochondria function, we think that that might be one of the targets that people will be able to notice.

David Roberts:

Great.

Dr. Martin Katz:

Yeah. There's a fairly large and probably increasing amount of literature showing that one of the biggest reasons we age is not being able to handle glucose very well. And certainly this lovely product, high fructose corn syrup, or just fructose in general. And so if you can put a molecule on the market that's going to affect that, that's going to be quite large. But again, from my perspective, there nothing like exercising while eating well. And there's a whole host of data on that, but certainly that's the way to go.

Dr. John Gildea:

When you think about just the very simplest version of exercise, most people, at least I can tell if I've exercised, I sleep better. And that's probably linked to when you're exercising, you're burning up your glycogen in your muscles and liver, and that's just making room for your glucose to go and be sequestered. It's that giant sink that's never filled, and exercise is a big one of those. And I think anything that can generally lower your circulating blood glucose levels will have positive effects on longevity.

Dr. Martin Katz:

Yeah, and it's interesting, just that utilization idea. Again, if you're not utilizing, but you're continuing to fill the sink and the sink gets blocked. And again, you mentioned something about too much fat in the diet, increasing aging, again, I think it's more caloric based and lack of exercise that the effects show there. So again, it's not just fat, it's the amount of calories and the lack of movement, and then you block that sink. Now you're not utilizing glucose because it's not getting into the cells, not being utilized correctly, and it's sitting outside affecting the blood cells, affecting the nerves, affecting the endothelium, and you wonder why you're aging and not feeling well. Well, there you go.

David Roberts:

There you go.

Dr. Martin Katz:

And you deserve to feel well, David and John.

David Roberts:

Yes.

Dr. Martin Katz:

You should. And we want to.

David Roberts:

Well, this has been helpful. Thank you. Thank you for this conversation. John, when can we expect maybe a little info on synergy with this product, resveratrol?

Dr. John Gildea:

Yeah, I'll give that a look and I'll pull some papers that, I don't remember them right off the top of my head, but that rang a bell. That usually means that there's a more than one paper there.

David Roberts:

Great. That sounds good. All right, everyone, thank you so much for listening. You've been listening to the Mara Labs Podcast. We'll be out next week with another show. Thanks so much for your time.

Dr. Martin Katz:

Thank you. Take care of your human.

Dr. John Gildea:

Bye.

David Roberts:

Bye.