David Roberts:

Hey, everybody. This is David Roberts, and you're listening to the Mara Labs Podcast. Today, I have Dr. Martin Katz and Dr. John Gildea with me, and we will be talking about resveratrol. We had a podcast in December where we talked about resveratrol, and since then we've released our version of resveratrol called ResverElite. There have been numerous questions that have come in. We want try to tackle at least a few of them but also just share some things we've learned that we didn't know even back in December as we've been doing our own internal research. So welcome, gentlemen.

Martin Katz:

Glad to be here, for sure.

John Gildea:

Exciting.

David Roberts:

So we've released our ResverElite, and we've had some folks trying it. I've tried it. I've been trying it too. I don't know if you have been trying it.

Martin Katz:

I have not yet, actually.

David Roberts:

Well-

Martin Katz:

I'll bottle up today.

David Roberts:

... we'll get you a bottle today.

Martin Katz:

Yeah.

David Roberts:

And so, one of the main questions that has come in that I'd love to hear from you about but also just hear your thoughts in general since we recorded two months ago, one of the prevalent questions has been, how is ResverElite different than our other products? Maybe we can do a comparison because there's certainly some overlap, but then some contrast as well at that. We can just dive in.

Martin Katz:

Yeah. I mean, again, this process of aging and process of disease is not a from zero to one, it's a fairly large scale, going across. And as I've mentioned numerous times before, I have so many patients coming to my practice who are clearly not healthy, but because they don't have the diagnosis of disease yet, which is the way our healthcare system works, everybody waits until they're diagnosed with

hypertension, or diabetes, or, God forbid, heart disease, or some type of neurodegenerative disease or something else, they don't think they're unhealthy. But again, if you look at, say, a car from empty to full, empty being no disease, full being full of disease, that's a fairly large scale. Again, at any point you can put things back in the tank that will reverse that disease. That's ultimately what I'm trying to impress upon you guys, as well as my patients, my family, people I love and have access to.

And so these molecules that we're introducing have a pretty big impact in those disease processes. We looked at those, that process from healthy to unhealthy. There's inflammation that has a lot of play, there's oxidative stress, and there's all these molecules that play into those processes. Then there's also aspects of a cell losing its ability to know who it is and what it is and what it's doing. There's molecules within that that help. That's where I'd put resveratrol. Our oxidative stress product, certainly sulforaphane. Our anti-inflammatory product certainly is curcumin. I would say BerbElite has, we've discussed it in numerous ways, many different properties that make it very beneficial. CurcElite, same thing. SleepElite, obviously, I think it speaks for itself.

Then when you come to resveratrol, it has a lot of the similar benefits to curcumin and sulforaphane in that it has some effect on Nrf2, it has some effect on NF-kappaB, but it has amazing effects on the sirtuin access, which David Sinclair has done a lot of work with. And then it also has effect on the nitric oxide pathway, on cardiovascular health with regard to lipids. So it's a molecule that, again, can add and work synergistically with these other molecules that we've put out that really have a lot to do with reversing this process of health, disease and moving the needle back towards health. And I think that's important.

David Roberts:

So, does resveratrol increase nitric oxide?

Martin Katz:

It does seem to have an effect on nitric oxide and the whole access within the ADMA sertraline access where the blood vessel's relaxing and having effect on blood pressure and cardiovascular disease. So it does seem to be protective. The other thing, that nitric oxide, again, can be bad when you mix it with these lipo peroxidases, these lipid oxidants where they can get in the wall of the blood vessel and create disease. And resveratrol does a good job of limiting those stress molecules.

David Roberts:

John?

John Gildea:

Yeah. I think that picture that you were drawing is really clear is that in each of these pathways there's one molecule that is notorious for being the best at regulating that pathway. So for sulforaphane, it's Nrf2. For curcumin, it's NF-kappaB. Berberine has big effects on blood glucose. But there's overlap between them. And so I have it in the category of, like you were saying, in the SIRT pathway, AMP kinase SIRT mTOR pathway, which is part of aging. So this one, more than other ones, is relating to pathways that traditionally in the model organisms were showing changes in longevity.

So that enters a different ballpark, which kind of makes sense because at least now as this field is mature, the human clinical studies are starting to come out. And the big effects for resveratrol seem to be in cardiovascular disease. So there's been a couple of pretty recent meta-analysis for cardiovascular disease, and that's probably because of the combined effects that it has. A single molecule seems to

touch on a number of different pathways, but its main one is cardiovascular disease. And it would make sense that that would show up as longevity because delivering oxygen and nutrients to your cells is in the middle of every healthy cell. So eNOS, there's endothelial NOS, and that's what it seems-

Martin Katz:

Nitric oxygen synthetase. Yeah, something-

John Gildea:

Yeah. So the enzyme. So just even a little bit of background on that, is that there's the microbiome derived NO and then exercise induced NO. And then is endothelial NOS, eNOS, one of the three nitric oxides synthases, and it's right in the endothelium where a lot of the damage from our current lifestyles seems to reside. And so vasodilation being a primary thing. And I think the second one that I would put it into a unique category is for PGC-1alpha activation. And that might be a newer topic for us, but it's a nuclear encoded transcription factor that has its effect out in the mitochondria. So it seems to be the master regulator of mitogenesis and mitochondrial function. So the fact that it is a vasodilator and increases mitochondria, that combination is really potent for affecting those, the lining, your blood vessels where, I mean, I think that's correct that that's the number one disease in humans in the current time.

Martin Katz:

Endothelial dysfunction. Yeah. I mean, I think that plays in beautifully to aging, because if you look at a lot of the data, it would suggest that muscle build and muscle maintenance extremely important to utilize that glucose so there's less glycation and mitogenesis, mitophagy being very important, the health of the mitochondria. And so if you can add to that with a molecule, that's extremely important.

And the other interesting thing that you bring up, John, is this idea of cardiovascular health. And my reading, I'd say resveratrol comes up pretty strong with Alzheimer's or neurodegenerative diseases as far as what it can do for limiting these tau proteins or, sorry, these amyloid proteins, and that, obviously, there's a lot of similarities. A lot of people are considering Alzheimer's the cardiovascular disease of the brain. So a lot of positives there too with what it does there.

David Roberts:

And then in terms of, we talked some in our last episode on resveratrol on dosing. So now we have ResverElite. We say take two a day. Let's say somebody has something, like they're trying to... What would be too much of our product given that it is so bioavailable?

Martin Katz:

Yeah, that's a great question. It really all depends on what else the person's doing and what else, what other medications, the person's on. In the studies where resveratrol for blood pressure was shown to be effective at 150 milligrams or more, which was pretty low, for sure, less than that you're not going to get much benefit with regard to blood pressure, the studies would suggest more than five grams you're going to be running into a fair amount of side effects at that point, and there doesn't seem be much more effect above five grams. 2.5 seem to be fairly safe, so 2,500 milligrams or 2.5 grams. Again, it really depends on what the other person's taking with regard to supplements because it does go through the liver. It's metabolized in the liver, the cytochrome P450 CYP enzymes.

And so if you're on a lot of different supplements, certainly if you're on certain meds like statins or certain calcium channel blockers, certain medications for immunosuppression, or if you're unfortunate enough to have cancer and certain cancer meds, you would have to be careful with this med because it can make those meds more bioavailable, more of them. So you may have more side effects from those other meds. It works really well on platelet aggregation. So if you're on a blood thinner, you want to be a little careful because you may bleed a little more on this medication. So I would say it has amazing benefits, but I would say talk to your physician before starting it and making sure you understand which meds are going through the liver. So maybe you'll take a lower dose if you're on some of those meds. And if you're not, then you can certainly follow our recommendations. Or if you're having certain disease processes happening more acutely, you can maybe up the dose for a short period as long as you're below 2.5 grams. I always get confused between those grams and milligrams.

David Roberts:

John, over to you.

John Gildea:

Yeah. To add to the possible-

Martin Katz:

Confusion?

John Gildea:

... side effects. Yeah. No, that was super clear. And the doses do seem gigantic compared to the original studies where they're thinking that resveratrol would work in the amount that's in a glass of wine. We're well past that. And-

Martin Katz:

Yeah.

David Roberts:

We're well past that, and that that's rubbish.

John Gildea:

Right.

David Roberts:

That the red wine resveratrol benefit is no longer believed.

John Gildea:

Right.

David Roberts:

Is that correct? Okay.

John Gildea:

Yeah. So then beyond that, I think the only negative studies I can remember seeing, besides the high doses, is blocking response to athletic performance. So that's the classic. It is a direct antioxidant. And so if you get it high enough in the bloodstream during the exercise, then you can blunt some of the effects that exercise has, beneficial effects of the stress. And opposed to some other supplements, this one seems to be the longer duration exercises. So if you do slow, long running, it would tend to block the beneficial effects of that, or things along that line.

So those are only the big negatives I've seen. And for the most part it's pretty short-lived molecules. So just don't take it close to when you're going to perform that endurance type exercise and I think you should be okay. And even in the case of recovery, since you're stimulating mitochondrial function and eNOS, normally eNOS activation or NOS activation during exercise would be beneficial, you have more blood going to your muscle, more blood going to your skin. The analogy of the radiator, of having blood go through your muscles to cool it and to your skin to cool, that the blood would have the beneficial effect of cooling, but that that's counteracted by the fact that you're not going to benefit for it. So say performance day, it could be beneficial to take it with an endurance event, especially because of the cooling. That's one of the big reasons that keeps you from continuing to exercise that full capacity is the overheating. It has a big effect on making you stop as your muscles are overheating. But for routine exercise, I would take it away from your exercise within at least a couple of hours.

Martin Katz:

Yeah. And just to further that understanding, exercise is one of those things that we do to adapt. So we're stressing things out. And so we want that hormetic stress to help us adapt to be stronger, to be more athletic, to learn certain movements, to be able to do certain movements better and persist through those movements. And so if you're taking a supplement that blocks that hormetic effect or that adapting effect, it's not always beneficial. But, yeah, I would tend to agree with you, if you're taking it away from it. It's similar to a lot of these anti-aging folks take metformin, and metformin seems to have a similar block. So people either take lower doses, take it away from when they exercise. Metformin has a more immediate effect. And then there's the metformin that's more prolonged. But resveratrol would be a more immediate effect.

John Gildea:

Yeah. It's probably good to just mention, too, that nitric oxide is an unpaired electron, so it would be considered an oxidant. So when you were talking earlier about dosing, this NO would be the same. There is a beneficial amount, and then extreme amounts of NO going unchecked can have deleterious effects.

David Roberts:

And that goes back to the dosing. So you were talking about the 2.5 grams of straight resveratrol. Of course, ours gets through the gut barrier. More of it gets through the gut barrier. Yeah. And we say take two capsules. If somebody wants to take more, is four capsules okay a day, six? Where are we on that? Where do we land on that?

John Gildea:

I mean, it's hard to compare the two because, I mean, even though straight resveratrol has been shown to have blood sugar effects, it's similar to berberine, and that usually takes-

Martin Katz:

Months.

John Gildea:

... weeks to months before you see the effect. Resveratrol is the same way. It does have beneficial effects there, but when you get it bioavailable enough, you can actually see acute effects on blood glucose. So both-

David Roberts:

Which we have.

John Gildea:

Yeah. So it does affect blood glucose directly. And that's also something to keep in mind. If you're trying to regulate your blood glucose, you should be aware that what Martin was saying earlier about checking with your doctor, if the effect is that obvious, then it's hard to make comparisons to how much you should be able to take at a time. Because I put it in kind of a similar category to curcumin in that curcumin has known antimicrobial effects, and berberine the same way. I would prefer it to be absorbed in the small intestines and not go down to where you're trying to cultivate your microbiome. So big effects long term on your microbiome I don't think have been studied real well. And it's better to get it absorbed earlier in your intestines where you're not having the effects on your microbiome.

David Roberts:

And this came up recently, so I've always taken resveratrol during the day and avoided taking it at night because I've heard, but I don't have a paper to point to, that it could mess with your sleep cycle, and just wanted to throw that out. Have you guys heard that? Is this a old wives' tale? And do you take it at night?

John Gildea:

So I tested it directly because I wanted to know that, and I slept deeper.

David Roberts:

Ah, okay.

Martin Katz:

I mean, if you look at the effects it has on the brain, that would make a lot of sense. But again, I haven't taken it yet.

David Roberts:

Yeah. Come on, Martin. Martin, sure, come here.

Martin Katz:

Thank you.

John Gildea:

And I think the mechanisms for the blood glucose and things I think are different for each one. Like, sulforaphane is known to lower blood glucose levels. But I think primarily, at least from the literature, it seems to be through blocking gluconeogenesis in the liver. In berberine it seems to be affecting, in my opinion, downstream signaling where c-Myc is a carbohydrate response element and it blocks utilization of glucose. So it's changing metabolism by changing the transcriptional state of the cell. Where I think in resveratrol it's affecting mitochondrial function. So I think those would be separate pathways and could potentially be synergistic. But I think when you start combining very potent supplements together, you should do it adding one more at a time and making sure everything's going well before you say two is good-

Martin Katz:

All on board. Yeah.

John Gildea:

... 10 is better. Yeah.

Martin Katz:

Yeah. Yeah. I would be careful with more than four capsules, even in acute state. Certainly, on all these I'm more conservative. I think you've taken as many of 10 sulforaphane, or somebody in this building has. I'm nowhere close to that.

David Roberts:

John, when you took your ResverElite at night, did you take other supplements as well?

John Gildea:

I've taken it with and without the SleepElite. So it does seem to enhance it beyond SleepElite.

David Roberts:

Okay, great.

Martin Katz:

N over one.

David Roberts:

N over one. Hey, it's valid.

John Gildea:

Good for me.

Martin Katz:

It's good for the goose, good for the gander.

David Roberts:

And then any other studies you guys have read recently that you want to bring up since our last podcast in December?

John Gildea:

I think for me the big one is, of course, everyone's trying to connect it to viral disease states. And so I think one of the interesting ones is that resveratrol's been connected to expression of ACE2. So not to get into a big discussion about ACE2 and viral disease, but I think it's pretty clear after all the dust settled that low ACE2 is bad, high ACE2 is good, and that it's this balance in the renin-angiotensin system. And when ACE2 is blocked, you're also blocking a beneficial arm of the renin-angiotensin system. So I have a direct connection with that just because of knowing that Ang-2 lowers testosterone. And so increasing ACE2 would increase the counterpunch to Ang-2. And it could be that that's the blood pressure lowering effect as well, but it's connected with testosterone production too.

David Roberts:

So resveratrol, basically you're saying that because it increases ACE2, it's connected to testosterone boosting as well?

John Gildea:

Yeah.

David Roberts:

Right. That's a benefit.

Martin Katz:

Yeah. I'm always talking about things that kill us, and I was reading about resveratrol decreasing, I can't remember right now if it was in rats or mice, unfortunately, and I also don't remember the dosing. I think the dosing was about 20 milligrams per kilogram, but it lowered LDL oxidized significantly. And if you look at LDL, and there's tons of that out there, people with low LDLs, that's low-density lipoprotein, it's for years been called the lousy part of cholesterol. But we're realizing that people with low LDLs have heart attacks and people with high LDLs do not have heart attacks. And so there's a lot more to this LDL picture than just, "Here's your LDL, and take a statin," basically. And-

David Roberts:

"Shut up and take a statin."

Martin Katz:

"Shut up and let's put it in the water." And so there's a lot more. And LDL oxidized is certainly one of that picture. So when LDL makes it through into the endothelial space and is oxidized, that's what tends to get those macrophages excited and starts these foam cells. And so if you can decrease that LDL oxidized molecule and have it be seen by the macrophages as something that's to be attacked and create these inflammatory plaques, these soft plaques, possibly inflammatory plaques that have a much greater tendency towards rupture and cause the heart attacks and the strokes, you can decrease that LDL oxidized, that's pretty phenomenal. And so that paper really impressed me with regard to resveratrol.

David Roberts:

Can we get that for the show notes?

Martin Katz:

Absolutely. I'll have to remember where I saw that.

David Roberts:

Before you leave the building.

John Gildea:

It's funny, that sparked a memory for me too, that one of the most impressive papers where I was convinced that after the big push early on in the '90s and early 2000s where dosing was called into question and also whether SIRT1 was a real target of it, there was a study done in monkeys, and it was a dose that was comparable to a supplemental dose and showed in the monkey that with high fat and high sugar, you got stiffening of the arteries and these atherosclerotic plaques where you can measure that lipid accumulation. It's kind of characteristic of chronic disease. And it reversed it almost 50%. I think I remember that-

Martin Katz:

Wow.

David Roberts:

Wow.

John Gildea:

... for me was a big turning point, that this has real big effects on real world cardiovascular disease.

David Roberts:

So I want to veer slightly and talk a little bit before we close about David Sinclair's research on anti-aging. So resveratrol is part of it. But can you guys, either of you, walk us through? I mean, he's really working on not just slowing aging but reversing aging. That's my understanding. And can you give us the broad brushstrokes of that research and how that's happening?

Martin Katz:

I'm going to leave this to John. John does a great job with his SIRT access, et cetera.

John Gildea:

Yeah. I think the big one there is basically that it's this whole connection to NAD. So NAD+ is the currency for chromatin regulation. It's the power source in that. And so if you get double-stranded breaks in that area, then it uses NAD. So for a long time, Sinclair has been famous for connecting NAD precursors or NMN and resveratrol so that you can get that beneficial one two combo on chromatin regulation or epigenetics. And so the general idea, I know I've said this a number of times, but if you get double-stranded brakes, it distracts your molecular machinery from remembering who you're supposed to be, transcriptional memory, into repair zone. And every time that happens, you've distracted that

machinery from it remembering who it's supposed to be. And so in that realm, there's a lot of markers now that are really beneficial called DAMage.

So DNA methylation tells you the on and off chromatin state of all the genes in your genome. And there's a number of those tests that are chronic disease states versus biological age states. And he's done some really seminal work in that area where these, what are called Yamanaka factors are how you make pluripotent stem cells. If you just subtract out of those four classic Yamanaka factors, subtract out the c-Myc because people think that activation of c-Myc will promote cancers and teratomas. So he puts in the other three OSK component of Yamanaka factors, and he's reversing those methylation points that are part of aging. And so we have a measure of aging now, and then we have these inducible factors that can reverse that methylation form of aging. And there's been some pretty crazy experiments showing reversal of this methylation dependent aging with sirtuin activation.

David Roberts:

Have either of you guys done the aging test?

Martin Katz:

I've not.

John Gildea:

Nope.

Martin Katz:

That's coming soon, for sure. Yeah. Hey, John, do you know what he's studied? I mean, he obviously started with worms and flies, so to speak. Do you know what he's most recently been looking at? Mice? Rats?

John Gildea:

So the ones that I'm aware of, I know there's a new study that I haven't closely read yet, but the big one that shows for me is this optic nerve crushing experiment. And so what he did was he has this adenovirus that has the three factors for the Yamanaka factors, and then he crushes the optic nerve and then shows that they're able to repair. And this is central nervous system tissue that's not supposed to ever repair. And so he gets reversal of this optical nerve repair, and it regenerates and then is able to actually gain function back in nerve tissue that's never been shown before. So that's-

Martin Katz:

And he did this on a plate, or he did this with-

John Gildea:

Mouse.

Martin Katz:

Mouse. Wow.

John Gildea:

Yeah. So I think the idea there is during that same set of experiments he did in cell culture and was able to show that even in cell culture, the cells do age as you passage them. And if you put in these three factors, they reverse this epigenetic aging that is going on. And so as a therapy in the future, it's really promising.

David Roberts:

That's great. Yeah, we can talk more about that maybe in another podcast, but I did want to touch base some on it now given how interesting it is. And I think we've talked, we've alluded to it, some before. But maybe we can get all of our ages done, see where we're at.

John Gildea:

That'd be cool.

David Roberts:

Yeah. Martin will be 12.

Martin Katz:

Mentally or physically? That would be the question for my family.

John Gildea:

That's why we have to do brain tissue.

Martin Katz:

Yeah. Yeah.

David Roberts:

Great. Well, gentlemen, thank you so much for your time today. And the listeners, thank you for your time. You've been listening to the Mara Labs podcast. We'll be back next week with another episode. And take care.

Martin Katz:

Take care of your human.

John Gildea:

Bye-bye.