

TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Matt Candeias	And I'm Matt Candeias.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	Crossover edition!
Matt Candeias	With In Defense of Plants!
Erin Welsh	Yes! I'm so excited.
Erin Allmann Updyke	Really excited. We've been waiting a long time, I can't believe this is the first one we've done this season.
Erin Welsh	We did ricin.
Erin Allmann Updyke	When was that?
Matt Candeias	That felt like forever ago by the way.
Erin Welsh	Yeah.
Erin Allmann Updyke	I think it was like like 7 years ago.
Erin Welsh	Easily.
Matt Candeias	Yeah. Much has changed in the meantime.
Erin Allmann Updyke	I don't remember anything about ricin, I gotta tell ya. I should listen to that episode.
Erin Welsh	Come on, the umbrella pellet?
Erin Allmann Updyke	Oh yeah, okay. Wow, cool.
Erin Welsh	A bad seed.
Matt Candeias	I thought about it yesterday when I was covered in ticks.
Erin Welsh	Oh yeah! That's right.
Erin Allmann Updyke	Okay now I remember. Thanks for reminding me.

Erin Welsh: There's so much, I feel like if somebody drew up a pop quiz of like 'Facts I Learned On TPWKY' I would fail.

Erin Allmann Updyke: That'd be embarrassing.

Matt Candeias: I had someone write me the other day and say, 'In one episode you said this but then in another episode you contradicted your perception on that.' I was like I don't know, i changed my mind I guess? I don't even remember saying that but cool, thank you for paying attention.

Erin Welsh: (laughs) Well what are we talking about on this very exciting crossover episode?

Erin Allmann Updyke: We're talking about the thing keeping me alive right now and that is caffeine.

Matt Candeias: Ah, my heart just swells when you say it.

Erin Welsh: I mean when you guys were reading about this or researching this, how much were you craving coffee or tea or chocolate or whatever it was?

Erin Allmann Updyke: I have had no less than 6 cups of coffee in the last 36 hours in which I have also had less than 2 hours of discontinuous sleep.

Erin Welsh: That doesn't sound great, Erin.

Matt Candeias: Ooh yeah, mental health. Take care of yourself.

Erin Allmann Updyke: We can talk about why it works though, it's gonna be really exciting.

Erin Welsh: Why it works for now.

Erin Allmann Updyke: Yep.

Matt Candeias: Well I did all my research in the morning while I was drinking coffee so it was perfect.

Erin Allmann Updyke: Excellent.

Erin Welsh: So to celebrate this wonderful thing to which we are all, I can assume, addicted, what are we drinking? What's our quarantini?

Erin Allmann Updyke: It's The Caffiend! Get it?

Erin Welsh: Yeah.

Erin Allmann Updyke: Erin, what's in The Caffiend?

Erin Welsh: It's kind of like a take on a White Russian so it's vodka, it's got Kahlúa, it's got chai tea syrup, cream, and then to make it even more caffeine-friendly we're gonna toss in a swirl of chocolate syrup on top and then garnish with a cinnamon stick if you have one.

Erin Allmann Updyke: Yum. That sounds so good.

Erin Welsh: I'm not sure that I do so...

Matt Candeias: I'm allergic to cinnamon so no, no.

Erin Welsh: Entirely?

Matt Candeias: Yeah. It's a tragedy. Pure tragedy.

Erin Allmann Updyke: Oh man. We'll post the full recipe for that quarantini as well as our nonalcoholic but still caffeine-friendly placeborita on our social media channels and our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com).

Erin Welsh: We sure will. So we just did an awesome interview today, it was so much fun with Corey from OPP which is Other People's Podcast. It's a podcast where he interviews other people about their podcasts.

Erin Allmann Updyke: It's super fun.

Erin Welsh: It's really fun, it was such a great experience, you guys should go check it out.

Erin Allmann Updyke: Yeah. Thanks for having us on, Corey, it was so fun.

Erin Welsh: All right. So now is that business done? Taken care of?

Erin Allmann Updyke: I think we took care of taking care of business.

Erin Welsh: TCOB. (laughs)

Erin Allmann Updyke: This is gonna be a great episode.

Erin Welsh: Well I think we already need a short break, maybe?

Erin Allmann Updyke: I definitely think so.

Erin Welsh: All right. We'll do that and then we'll come back with some caffeine.

TPWKY: (transition theme)

Erin Welsh: Okay. The story of caffeine. So when I was preparing this I was like okay, I don't know if I should concentrate more on coffee or tea or cacao or any of the other caffeine-containing plants or foods or beverages that we consume. And I'm sure Matt, you'll talk about some of those other ones.

Matt Candeias: Yeah, a little.

Erin Welsh: And then one thought that occurred to me was maybe I'll write out a different history for each of those. I'll write out a thing for coffee, I'll write out thing for tea, and I'll write out a thing for cacao and I'll be like, you guys choose, you can choose your own adventure.

Erin Allmann Updyke

Ooh.

Erin Welsh

And then I was like why would I do that to myself?

Erin Allmann Updyke

(laughs) Good question.

Matt Candeias

Each one of those is a novel in and of itself, all right.

Erin Welsh

Yeah! This is why I struggled. So instead I decided to just do a very general overview of caffeine, mostly concentrating on the big hitters, coffee and tea with a little bit of cacao thrown in there.

Erin Allmann Updyke

Awesome.

Erin Welsh

So I wanna start by just going over a little bit of the origin stories, the best part of every superhero movie. So let's start with tea. So tea was supposedly discovered by Shennong, the mythical first emperor of China and the inventor of all kinds of things from animal husbandry to the plow to plant-based medicine and of course tea. And so the story goes a little something like this. One day Shennong sat down under a shady shrub to escape the heat in a particularly hot day and then he decided to cool off by building a fire. I don't understand how that would work. And then boiling some water to drink. Again, doesn't seem like a particularly cool-down experience.

The boiled water thing actually did make sense because he had noticed that people who boiled their water tended to get sick less often which is pretty cool. But as he was building up his fire by adding more branches, a few of the leaves on the shrub that he was sitting under, they just happened to fall into his pot of boiling water. And he was like, 'You know what? I'm not dipping my hand in there and scooping them out, I'm just gonna let them stay in the water.' And then he drank it and he was like, 'What is this? This is delicious, I wanna drink more of this, I need to tell everyone about this.' And of course it was tea.

Erin Allmann Updyke

Can I just say that story reminds me a lot of the willow story of the guy trying to take a rest behind a tree and then chewing on some bark and being like, 'Ooh, my pain is gone!'

Erin Welsh

Yep, yep.

Erin Allmann Updyke

Oh how fun!

Erin Welsh

(laughs) Always these fortuitous discoveries that just somehow...

Matt Candeias

Under trees!

Erin Welsh

Under trees!

Matt Candeias

If you're stumped, you know where to sit.

Erin Allmann Updyke

On a stump!

Erin Welsh

(laughs) Oh that was so dorky, I liked it.

Matt Candeias

I'm for it.

Erin Welsh

Okay so also in addition to being the discoverer of tea, he also recognized a lot of the stimulatory - is that a word? - properties of tea. So he actually kept track of his own medical records so they were like hundreds of pages of his own like, 'This is what my bladder was like, this is what my temperature was, whatever, this is what the bile was.' But he wrote down in his records that tea was good for tumors or abscesses that come about the head or for ailments of the bladder. It dissipates heat caused by phlegms or inflammation of the chest, it quenches thirst, it lessens the desire for sleep. It gladdens and cheers the heart. Also true.

Matt Candeias

And how.

Erin Welsh

And so because of these amazing benefits of tea, this drink steadily grew in popularity in China and then it downright exploded during the Tang Dynasty between 600-900 CE. But outside of China the first references to tea come from about 900 CE in writings by Arab traders. But no one in Europe or the New World or anywhere else really knew that much about tea or cared to investigate it further until the mid 1500s despite the fact that there was ample trade going on. But remember that date, mid 1500s.

Erin Allmann Updyke

Okay.

Erin Welsh

Okay. So now coffee. The coffee bush, as I'm sure you'll talk about maybe Matt, grows throughout Africa and that's probably where it originated, like Ethiopia area.

Matt Candeias

Yeah I've heard sort of Middle Eastern Africa.

Erin Welsh

Middle Eastern, Yemen, Ethiopia areas. But it doesn't seem that coffee was used by or even known to anyone in any of the ancient worlds, so like Ancient Greece, Ancient Rome, Ancient Middle East, or Ancient Africa. There is some evidence that in Ethiopia coffee beans were first consumed by people possibly as small balls consisting of the ground fruit and then the bean itself and then packed together with lard to make a little energy ball.

Erin Allmann Updyke

Energy bites?

Erin Welsh

Energy bites.

Matt Candeias

Nice.

Erin Welsh

I mean I have always loved eating chocolate-covered coffee beans and then I find myself being like why can't I sleep? Why do I feel so... What's the word, alert?

Erin Allmann Updyke

On edge?

Erin Welsh

On edge, yeah.

Matt Candeias

My grandmother used to give them to me as a kid and she would call them goat turds. She was like, 'You want some goat turds?' And eventually I learned that yeah, I do.

Erin Welsh

(laughs) Like that's not gonna put me off them.

Matt Candeias

Yeah, welcome to my life.

Erin Welsh

Well and then there's the whole thing about the civet and the most expensive coffee in the world is the one that has been passed through a civet's intestines, bowels.

Erin Allmann Updyke

Poop.

Erin Welsh

Yeah. Anyway, okay. And so there are some historical references to ancient documents or accounts of coffee drinking as early as the 6th century but the earliest indisputable records puts that timing as no earlier than the middle of the 15th century in the Sufi monasteries of the Yemen in Southern Arabia. And this story goes a little something like this. An Ethiopian goatherd name Kaldi was out herding his goats one day when he noticed his flock nibbling on some bright red berries on a certain bush. And they wouldn't come over when he called but when he found them they were all jumping kind of frantically and frenzied dancing around.

He was like, 'Okay it has to be something with these red berries on this bush. So what would happen if I tasted them?' So he chewed on some of the berries himself and he liked what he tasted so he's like, 'Alright, I'm gonna gather a handful of these and bring them to the nearby monastery.' But the holy man of the monastery did not approve of these devilish red berries and so they threw them into the fire which then only led to the most delicious smelling aroma. And they were like well, not so fast. So they dragged these beans from the ashes, ground them up, and then dissolved them in hot water leading to the first cup of coffee.

Matt Candeias

Weird.

Erin Allmann Updyke

What an interesting story.

Matt Candeias

There's so many steps in there, I would've loved to see sort of the thought process.

Erin Welsh

(laughs) Back to the fire you must go! So I mean of course this story just as the one previous might just be a story.

Erin Allmann Updyke

Right.

Erin Welsh

But somehow the infusion of both tea leaves and coffee beans had led to this discovery that whatever the infusion was was delicious in some way even though it's bitter and surprising that people found it that delicious but maybe that's just the power of caffeine. Okay, so now cacao. Cacao was first cultivated not by Mayans but by the Olmecs who lived in the lowlands of Mexico from around 1500-500 BCE. And they used the cacao pods to make a chocolate drink. And there's even evidence on a pottery jar from like 500 CE found in Guatemala that has hieroglyphs that indicate cacao and analysis of the contents of the pot showed traces of caffeine and theobromine.

Matt Candeias

Nice.

Erin Welsh

And the drink was called chocolatl of course. And then the Mayans after them, so the Mayans after the Olmecs, so around 1000 BCE to 250 CE followed the Olmecs in this using cacao as currency often. And then after the Mayans it was picked up by the Toltecs between the 10th and 12th centuries and then finally by the Aztecs from the 12th centuries until the Spanish conquistadors arrived in the mid 1500s and had chocolate for the first time and then destroyed everything.

Erin Allmann Updyke

Yeah.

Erin Welsh

And so also just a note on naming, when Cortes first arrived to start the fall of the Aztec Empire, he was given chocolate initially in this warm welcome and he was like, 'This is so delicious, this is the drink of the gods.' Hence Theobroma cacao.

Matt Candeias

Wow, I don't think I had ever put that together.

Erin Welsh

Okay so with tea, coffee, and chocolate I stopped at around the mid 1500s because that was in general the time when each of those stopped being known to only the region they originated in and that's when they began this worldwide tour of notoriety that would lead to caffeine consumption on a scale that has never decreased.

Erin Allmann Updyke

That is so interesting that all three kind of coalesced at the same time.

Erin Welsh

I think a lot of it has to do also with just the timing of when long distance traveling was made more possible and sort of as it coincided with as we talked about in the scurvy episode I think, there was all of a sudden a need to go trade more and shipbuilding really increased and that technology for traveling long distances increased. And then of course when you find something like this that is widely consumed in a certain area and found to be delicious, probably one of the things that first occurs to you is how can I make money off of this? How can I profit off this?

Erin Allmann Updyke

Of course, of course. Yeah.

Matt Candeias

And I mean we all use it for productivity, imagine when that started to catch on among all of the already crazy economic "progress" quote unquote that was happening.

Erin Allmann Updyke

Oh yeah.

Erin Welsh

Yeah, exactly. And so these of course began to be highly sought after particularly in Europe and in North America during the 1600s when colonialism was raging of course. And these caffeinated beverages may have come along at just the right time. So temperance movements in Europe had happened before, they had started and failed and started and failed long before coffee and tea came onto the scene. And they failed largely because the proponents of these movements didn't have an alternative beverage to suggest to replace alcohol. They were like, 'You need to stop drinking.' And they were like, 'Alright, maybe I will but what should I drink instead? Drink the poop-infused water? Like no, it's not good.' And so when coffee and tea and hot chocolate came onto the scene, alcohol at that time was consumed at every meal, breakfast, lunch, dinner, by every person in Europe whether you're a child or someone who's working or someone who's elderly.

Matt Candeias

Oh my god.

Erin Welsh

It was ubiquitous. And in a way alcohol was safer than the water because at it at least killed a lot of the germs. So when tea and coffee replaced the morning beer or the lunchtime pour, people saw a noticeable shift in the productivity and safety of the workplace.

Erin Allmann Updyke

I mean go figure.

Erin Welsh

I never even thought of it. And there's the fact that these beverages were boiled and so that also reduced the chance of getting some sort of water-borne pathogen or parasite.

Matt Candeias

What a massive cultural shift to go from being drunk all day to just drinking caffeine all day. That must have been huge!

Erin Welsh

Huge!

Erin Allmann Updyke

Yeah.

Erin Welsh

It's wild. And so these caffeine drinks, these caffeinated drinks have been credited with shaping the entire European workforce and leading to a burst of creativity and ingenuity, eventually that paved the way for the Industrial Revolution. Maybe that's a stretch but I don't know.

Erin Allmann Updyke

It's not a stretch, let's take it.

Matt Candeias

Let's say it made an impact and then some.

Erin Allmann Updyke

That is so cool.

Erin Welsh

Isn't that amazing? And these beverages were also held to be indirectly responsible for other kinds of revolutions, namely political ones.

Matt Candeias

Oh yeah.

Erin Welsh

So teahouses which had been popular in China since the 13th century CE, they started to become popular in Europe and in the New World as well and coffeehouses also sprung up and were incredibly widespread and popular. Like the amount of coffeehouses per capita was maybe only we now have reached it.

Erin Allmann Updyke

Wow.

Erin Welsh

And so for instance in England they were given the name 'penny universities' to describe how people - and men were only allowed into coffee houses at the time - how men would go to these coffeehouses to talk about philosophy or politics or to hear music or poetry. So in many ways they still exist in the same capacity today which I think is really interesting, like the open mic night at the coffeehouse.

Erin Allmann Updyke

Yeah, it's like a gathering place.

Erin Welsh

So some of the documentaries that I watched was like, 'You know, would the same political discourse be held at a bar and the same actions be planned in a logical way that they would be at a coffeehouse?' Fueled by alcohol vs fueled by caffeine.

Erin Allmann Updyke

Yeah.

Erin Welsh

When are you going to most get the ends that you're planning, I guess? I don't know.

Matt Candeias

Cool.

Erin Allmann Updyke

Fascinating.



Erin Welsh

Interesting to think about. There were still temperance movements but this time against coffee primarily and also tea, or it was alternatively coffee and then tea. But yeah, so back on the revolution thing, in the British colonies of the New World coffeehouses in Boston were essentially the headquarters of the American Revolution. The Boston Tea Party was planned at a coffeehouse called The Green Dragon and the first public reading of the Declaration of Independence was held at another Boston coffeehouse, The Bunch of Grapes.

Matt Candeias

Nice.

Erin Allmann Updyke

That's funny.

Erin Welsh

Kind of a fun name. And of course tea itself or rather the import tax on tea and the British government allowing the East India Company to also tax the import of tea on the colonists, that was all part of the reason for the American Revolution in the first place. And that also kind of brings me to the dark side of coffee and tea and chocolate. Yeah, always.

Erin Allmann Updyke

There's always a dark side.

Matt Candeias

Oh yeah.

Erin Welsh

There's always a dark side. So coffee and tea were both in incredibly high demand in European countries and in the British colonies in the New World but caffeine addiction was an expensive habit to pick up in those early days as the cultivation of the plants was pretty restricted. So anytime for instance that coffee beans were sent out from Mocha which is where they were primarily grown, they were made sure to not be able to be germinated or to not be able to grow into any viable plants. And it's sort of like what we saw with the cinchona bark in the malaria episode and restrictions on that plant being grown elsewhere. But eventually where there's a will, there's a way and so people did manage to smuggle out some coffee beans and a few tea seeds. And so coffee was smuggled from Mocha and planted in the Dutch controlled Java around 1616 and that as also found to be able to grow in many parts of the New World which had the right humidity and temperature and so on for the growth. And of course if you want to gather a lot of the coffee beans you have to gather them by hand. And what did that take was a lot of hands. And so what did that lead to but a lot of enslaved people being forced to labor under horrific working conditions on all these plantations in the New World. And of course as consumption and demand for coffee rose, so did the number of enslaved people. And the popular habit of adding sugar to coffee and tea ensured that sugar plantations also had a reason to exist, right.

Erin Allmann Updyke

Geez Louise.

Matt Candeias

Capitalism.

Erin Welsh

And while all this was happening, England was racking up a hefty debt to China in the tea trade and so they saw an alternative way to save some money and to try to limit how much they were giving in terms of bringing the tea over from there. So they were like well why don't we get some tea seeds and start growing tea plants in our colony in India which was all of India. And so Britain ruled over India at the time and so they planted tons and tons and tons of tea plants and they "hired", kind of putting hired in quotes because they literally paid them almost nothing, in back-breaking conditions. And then at the same time they also grew a bunch of opium and then smuggled that into China to then addict the whole country and drive them into ruin.

Matt Candeias

I had no idea.

Erin Welsh

There's a whole separate story of the Opium Wars and the East India Company, it's just a massive story there, it's really fascinating. But read more about it.

Matt Candeias

Wow.

Erin Welsh

I don't have any information. But anyway, so then because of this, because of all of the tea that had been able to grow in India, that flooded the market back in Britain and it toppled coffee as the preferred beverage.

Matt Candeias

Wow.

Erin Welsh

And then that also led to afternoon tea and then eventually tea bags and all these different cultures around tea. So anyway, the 1800s saw the continued popularity of these beverages and also 1819 saw the discovery of the caffeine molecule by a young physician named Runge.

Erin Allmann Updyke

Oh!

Matt Candeias

Wow.

Erin Allmann Updyke

1819, okay.

Erin Welsh

And then the next year four other researchers were able to isolate the compound. So it kind of happened all at once. But this discovery did not start the debate on the healthy or harmful effects of caffeine but rather continued it, this debate has been going on for ages and still seems to be raging. Erin, I'm sure you'll talk about that.

Erin Allmann Updyke

Oh yeah.

Erin Welsh

And there's just a little bit more of the history of caffeine that I wanna touch on. So caffeine played a huge role in the wars. It was during the Civil War, during WWI, during WWII, given to soldiers like unlimited rations of caffeine whether in the form of caffeine powder, whether in the form of unlimited tea, whether in the form of Coca Cola. And it often was restricted to try to reduce the morale of whatever opposing side was there, for instance that happened during the American Civil War. And then of course the 20th century saw caffeine in many different products, so we see the rise of it in sodas and then in energy drinks and then decaf and then advertising wars leading to basically the consumption and an entire world addicted to this compound which is also of course what then started a ton and ton and ton of research over the safety of caffeine.

But this was not a very well done history or whole history but hopefully what is has done is given you a little bit of the taste of just the massive impact that caffeine has had on the world's history and culture. And I wanna wrap up a little bit by saying there are some parallels between particularly coffee and tea. So I just wanted to find some patterns in these histories. So number one, both of these were harvested as a leaf or a berry and used as a stimulant or medicine first and they often held great significance for the culture where they were first used. Number two, each was only used as an infused drink relatively recently, so maybe starting in the 1500s. Number three, each was brought into the region that they are now associated with by religious devotees returning from another country. Number four, their cultivation was protected. And number five, they were used as currency. So coffee beans were used as currency in Arabia, kola nuts used as currency in Africa, cacao pods and mate leaves in the Americas, and tea leaf bricks in China.

And the final point I wanted to make is that number six, just as it has always been, in the present day the people who are actually farming and producing these products see a minuscule fraction of the profit that eventually comes out of them. So for every \$10 that you spend on a bag of coffee for instance, the farmer who produced it sees maybe \$1 of that and that's just how it is. There are some programs that seek to remedy that or seek to make it a little bit more fair but it's debated whether they actually function. So anyway, that's my story. Erin, please tell us why we are so addicted to caffeine and why right now just talking about it makes me wanna have a cup of tea or an afternoon coffee.

Matt Candeias

I was just thinking, do we have decaf?

Erin Welsh

I know, if I did have coffee right now I wouldn't be able to sleep for sure.

Matt Candeias

I'd be up all night, yeah.

Erin Welsh

Yeah.

Erin Allmann Updyke

So you guys wanna know why?

Erin Welsh

Of course I do!

Matt Candeias

Yeah.

Erin Allmann Updyke

Okay let's take a quick break and then I'll talk about it.

Erin Welsh

Excellent.

TPWKY

(transition theme)

Erin Allmann Updyke

Okay. So Erin, it's very interesting that you used the word 'addicted' because I think a lot of us think of caffeine as an addiction, 'I'm addicted to coffee, I'm addicted to coffee'. And it's true that caffeine is the most widely used by far psychoactive substance, drug, in the world. I think over 85% of Americans regardless of age use caffeine.

Matt Candeias

Wow.

Erin Welsh

Wow.

Erin Allmann Updyke

Right?

Matt Candeias

Dang.

Erin Welsh

Regardless of age.

Erin Allmann Updyke

Yeah so for adults it's a lot more than 85% and hopefully it's less kids but because that includes soda, right, and a lot of kids drink soda and chocolate.

Erin Welsh  
Which for a long time soda companies, namely Coca Cola, was like, 'Oh yeah, caffeine is a flavor additive, like it's required to be there because it's a flavor additive, it adds bitterness.' But in double-blind studies, people couldn't detect the difference and so it was like are you just doing this to addict the children to caffeine, tap into a whole new market? But then there's sugar so like is that addictive? You know, whatever.

Erin Allmann Updyke  
Yeah so there's no diagnosis of caffeine addiction and so whether or not you consider caffeine to be something addictive kind of depends on what the definition of addictive is which is a whole other debate that I'm not even going to get into. But it is true that caffeine has effects on your nervous system such that with habitual use, if you stop using caffeine you will experience things like withdrawal symptoms and so that means you can become dependent on caffeine which is something that's often part of a diagnosis of something like addiction. So let's talk a little about the effects of caffeine on your brain, okay?

Matt Candeias  
Yay.

Erin Allmann Updyke  
All right. We all drink caffeine, is that correct?

Erin Welsh  
Yes.

Matt Candeias  
Oh yeah.

Erin Allmann Updyke  
The three of us, okay. Tell me what it feels like when you drink a cup of coffee? What are your symptoms?

Matt Candeias  
I have to run to the bathroom really quick.

Erin Allmann Updyke  
(laughs) Okay, thank you for that honesty.

Matt Candeias  
Yeah, no, euphoria, excitement, heartbeats go up.

Erin Allmann Updyke  
Okay.

Erin Welsh  
Alertness. I always feel like I kind of have a beginning period of this feels great and awesome and I'm finally where I need to be in my morning and then my bones start to feel hollow and I get like... Is that not a thing? Where I feel so jittery.

Erin Allmann Updyke  
Jittery, okay.

Erin Welsh  
I have so many questions I'm getting ahead of myself. I'm like but I don't eat breakfast so does that have an impact? But mostly I feel like I'm talking right now which is a mile a minute, my brain's very focused.

Erin Allmann Updyke  
Okay, great. You guys are hitting on a lot of the effects of caffeine, okay. So it's a stimulant so it has an effect on your central nervous system. So the reason that it's able to have an effect on your CNS is because when you ingest caffeine, generally we ingest it orally right, so you drink a cup of coffee or you pop a caffeine pill or you sip a cup of tea and almost 100% of that caffeine becomes bioavailable. So you absorb it through your intestine and it goes into your bloodstream. Caffeine is a lipophilic molecule, so it can pass through lipid membranes which means it can pass through your blood-brain barrier and get into your central nervous system right away.

Matt Candeias

Whoa.

Erin Allmann Updyke

And within like an hour of consuming caffeine, your blood levels and your plasma levels are almost equivalent so it kind of distributes equally throughout your tissues including your brain. Okay so we know that it's overall going to keep you awake and now we know that it can get into your brain, so it's going to have some effect there. But the question is really what is it doing on a molecular level? And this is really fun. And I'm gonna keep it really pretty simple and basic because there's a lot of nitty gritty biochem here that I just don't have enough caffeine in me to get into that nitty gritty detail.

So what we need to know is that depending on the concentration of caffeine when we look in cell culture studies or animal model studies, we know that it can have a lot of different effects on cells, right. Like it interacts with cells and can cause a lot of different things when you look at them in an animal. But when you ingest it like your drinking a cup of coffee, the amount that you would ingest with that, there's really only one main receptor that caffeine is going to interact with and that is with the adenosine receptors. So adenosine might sound familiar, does it sound familiar to you guys?

Erin Welsh

Mm-hmm.

Matt Candeias

I've heard that word.

Erin Allmann Updyke

Why does it sound familiar?

Erin Welsh

ATP?

Erin Allmann Updyke

ATP.

Matt Candeias

Nice.

Erin Allmann Updyke

So adenosine triphosphate or ATP is the energy of all of our cells, okay. so when your cells use a bunch of energy like your brain for example, if your brain is working really hard because you're thinking or your muscles are working hard cause they're contracting. They use up ATP and in using up ATP they release or create essentially by taking off phosphate, they release adenosine which is the adenosine part of adenosine triphosphate, ATP. When adenosine levels in your brain become high they bind to a number of different adenosine receptors, there's a bunch of different subtypes, and they basically cause you to become sleepy. Because if you think about it, if your brain is working hard and using up a bunch of energy, then your brain probably needs a rest, right? So by using up ATP you increase the levels of adenosine which tells your brain by binding to these receptors, 'Hey, I'm tired, I need a rest. Let's take a break.' Okay?

Erin Welsh

Which is why at the end of the day that build up makes you fall asleep and you get sleepy at the end of the day.

Erin Allmann Updyke

Exactly.

Matt Candeias

Oh wow, the crash.

Erin Allmann Updyke

It's not the only thing, sleep is more complicated than that but that's one thing, okay. So yes. So caffeine as it turns out is an antagonist of adenosine receptors which means it blocks adenosine receptors. So if it blocks the thing that makes you sleepy, it makes you feel awake.

Matt Candeias

Amazing.

Erin Welsh

Question.

Erin Allmann Updyke

Okay. Can't wait.

Erin Welsh

So if you plotted the adenosine throughout the day starting in the morning of an average day and you averaged it or whatever, in the morning would it also be high because you're just waking up and you're not quite there? Why does caffeine make you wake up in the morning? Like I could see why it would throughout the day make you feel more awake as it blocks those receptors but why in the morning does it help?

Erin Allmann Updyke

Great question. So I don't fully know the answer to that, I don't know if maybe there's just adenosine leftover residual or if just by blocking those receptors you prevent any adenosine from binding. But I have seen some studies that suggest that caffeine has greater effects if you're already a little drowsy, right. So if you're already tired and then you drink caffeine, it has greater effects when they've done trials of how alert are you, what's your response time, things like that. The effects are greater if you're already drowsy rather than if you're already alert, if that makes sense.

Erin Welsh

So there's like a maximum alertness almost and then to get back to that maximum, coffee will help you get to there? I don't know.

Erin Allmann Updyke

It's complicated Erin, this is just the basics.

Matt Candeias

It makes sense though because I feel like anymore today, caffeine in the morning just kind of levels me whereas caffeine at like 2pm floors me, I'm like, 'Let's get this done!'

Erin Allmann Updyke

So another interesting point is that remember I said you can become dependent where you can have withdrawal symptoms? When you are a habitual user of caffeine, your body actually upregulates the number of adenosine receptors so that adenosine can still bind so that caffeine is actually less effective which we see with so many different compounds where you basically create tolerance to it, your body finds a way to get around this drug that you're giving it, right.

Erin Welsh

How long does it take to build a dependence or to actually see those physiological long term changes?

Erin Allmann Updyke

Not very long because you can have withdrawal symptoms after just maybe 3 or 4 days of chronic caffeine use. But it usually only takes 48 hours to go through withdrawals but for some people it can take up to 9 days.

Matt Candeias

Oh wow.

Erin Allmann Updyke

Caffeine's another thing that the effects of caffeine vary greatly depending on interpersonal differences in metabolism and things like that. So there's a huge amount of variation in the effect that a single cup of coffee is gonna have on any given individual.

Erin Welsh

I have a question.

Erin Allmann Updyke

Oh gosh, okay.

Erin Welsh: Okay so in terms of talking about withdrawal, why do we see some of the symptoms we see?

Erin Allmann Updyke: Oh, Erin.

Erin Welsh: When you have the excess of receptors, like I see how you'd be sleepier than normal or it'd be more difficult to wake up but why do I get a massive headache and I feel like killing everyone around me?

Erin Allmann Updyke: Great question.

Matt Candeias: Yeah.

Erin Allmann Updyke: Okay so let's talk about some of the other effects of caffeine to be able to understand that, thanks for asking.

Erin Welsh: I'm very excited.

Erin Allmann Updyke: That's perfect, okay. So the alertness and awakensness, that aspect right, this hypervigilance, increased alertness, which leads to things like faster response time, better driving, okay, if you're sleepy caffeine does make you a better driver, things like that. Those we can kind of all explain from the whole adenosine receptor thing. But that's not the only place that we have adenosine receptors is not just in those parts of our brain that have to do with sleepiness, okay. Adenosine has a lot of other effects on our body. For example there are adenosine receptors in our heart that block electric signaling in our heart. So for example if someone in the hospital has what we call a supraventricular tachycardia, so their heart is beating way, way, way too fast and out of proper rhythm, you give them adenosine, it blocks all electric conduction to their heart, stops their heart for a split second, and then they can restart a normal sinus rhythm. So if adenosine can stop and slow your heart rate, what do you think caffeine can do if it blocks those receptors? Increase that heart rate.

Erin Welsh: Yeah.

Erin Allmann Updyke: Okay. So that's an effect that you mentioned Matt, right, you feel your heart rate going up.

Matt Candeias: Oh yeah.

Erin Allmann Updyke: Okay. So headaches. Adenosine has also effects not just on your heart but on your vasculature. In your brain, adenosine can help vasodilate vessels to your brain while in your peripheral blood vessels it causes vasoconstriction. Don't ask me the details please but it does do that.

Erin Welsh: Why?

Matt Candeias: That was my next question, details!

Erin Allmann Updyke: So caffeine does the opposite. Caffeine causes vasoconstriction of your cerebral blood vessels to your brain and vasodilation of your peripheral blood vessels. Vasoconstriction is what a lot of headache medications do because a lot of headaches are caused by vasodilation, increased pressure in your brain, right, from too much blood flowing there. So if you have caffeine and can vasoconstrict those blood vessels, caffeine is really helpful and it's in a lot of headache medication, right, like what do you call that stuff? Excedrin.

Erin Welsh: Excedrin, yeah.

Erin Allmann Updyke: Right. And there's been a lot of studies that show NSAIDs with caffeine are more effective than NSAIDs alone for a lot of headaches. But on the flip side if you then take away that caffeine that your brain is used to having you're gonna have increased blood flow to that brain, you're gonna have a headache.

Matt Candeias: Wow.

Erin Allmann Updyke: That's pretty fun, right?

Matt Candeias: Yeah.

Erin Welsh: What about my hollow bones? (laughs)

Erin Allmann Updyke: Your hollow bones, okay.

Matt Candeias: You're a bird, stop it.

Erin Allmann Updyke: So I'm not sure this can fully explain the hollow bones necessarily but the jitteriness, okay. So this one's really fun. Adenosine in your brain also has interactions with dopamine receptors and dopamine release, okay. We've talked about dopamine a number of times on the podcast but dopamine is really important both in mood, so more dopamine usually means more happier but too much dopamine can also mean psychosis, so we think that things like schizophrenia have to do with too much dopamine, okay.

Matt Candeias: Wow.

Erin Allmann Updyke: But dopamine is also really important in motor control, right. So Parkinson's for example is a problem where your basal ganglia doesn't produce dopamine properly or doesn't respond to dopamine properly so you end up with slow movement and a resting tremor, okay. So adenosine normally is an antagonist of dopamine, so it blocks the release of dopamine. Caffeine is an antagonist of adenosine, so it increases the release of dopamine so it can cause those tremors, it can increase muscle contraction, so maybe that's part of it for you Erin and your hollow bones.

Matt Candeias: Wow.

Erin Allmann Updyke: It's why some people think that caffeine is a performance enhancer in general like for athletic events. People used to use caffeine, they still do I'm sure for like, 'It's gonna make me run faster.' There's not a ton of data that says it actually does, it really just delays exhaustion most likely. But you know, give it to them if it makes them feel good.

Matt Candeias: I'm calling the Olympics, that's a performance-enhancing drug.

Erin Allmann Updyke: You know there used to be limits on how much caffeine you could have in your bloodstream as an Olympic athlete.

Matt Candeias: Wow.



Erin Welsh: How much could you have?

Erin Allmann Updyke: That's a question for you. History.

Erin Welsh: That's so fascinating and it makes so much sense. Whoa.

Erin Allmann Updyke: Isn't it? And it also can kind of get at Matt why you said caffeine makes you feel happy, right.

Matt Candeias: Yes.

Erin Allmann Updyke: Caffeine can also increase serotonin levels in your brain. So some people think that it can maybe help with depression. There's not a ton of great evidence for that because we've kind of already talked about a lot of these symptoms, heart palpitations, feeling like you're jittery, that sounds a lot like an anxiety attack.

Erin Welsh: Anxiety, yeah.

Matt Candeias: Oh yeah.

Erin Allmann Updyke: So caffeine can actually exacerbate anxiety especially in people who already have anxiety or who are prone to panic attacks.

Matt Candeias: I've definitely had periods of my life where I've had to avoid it for that reason.

Erin Allmann Updyke: Yeah.

Matt Candeias: That's why when you were going through the history I was like I wanna meet the first person to overdo it on coffee.

Erin Allmann Updyke: Yeah, yeah.

Matt Candeias: Yeah.

Erin Welsh: Somebody, I can't remember who it was, used to drink, this isn't coffee but they would drink around 50 cups of hot chocolate a day.

Erin Allmann Updyke: Nope.

Matt Candeias: Ugh.

Erin Allmann Updyke: Bad idea.

Matt Candeias: I just got indigestion thinking about that.

Erin Welsh: Speaking of, why does coffee make you poop?

Erin Allmann Updyke: Okay.

Matt Candeias: Please tell me.

Erin Allmann Updyke

So poop and pee, right. So people say caffeine's a diuretic, it makes you pee and it makes you poop. I saw some things that suggest that maybe it can have some pro-motility effects on your bowels but in general my understanding is that that's mostly a timing association, most people poop in the morning, most people have coffee in the morning, any time you eat something, that's gonna kind of wake your bowels up, get them moving so then you can have a poop. The diuretic effect, so making you pee, there is some evidence that at very high levels there might be some diuresis from caffeine ingestion but in general especially at levels that you would consume normally, it's really a negligible effect. So it's really like are you drinking a liquid? Then you'll have to pee.

Matt Candeias

Oh wow. So the whole thing about coffee dehydrating the heck out of you is probably blown out of proportion?

Erin Allmann Updyke

Yeah, I think again with the tolerance thing, if you never drink caffeine ever then maybe it might have a little bit more of a diuretic effect than if you drink coffee regularly. But in general it doesn't really have as strong of a diuretic effect as we used to think.

Erin Welsh

Man, I am shocked about it not having a direct link to pooping.

Matt Candeias

Yeah.

Erin Allmann Updyke

Yeah, there was only like one paper that I saw that even mentioned its effects on GI. So I don't even know how real... I think it's largely timing, you know. You eat something, you drink something that wakes up your bowels.

Erin Welsh

I don't eat anything in the morning!

Erin Allmann Updyke

So even coffee has calories, right, and it's sending the signals to your stomach, it's activating those stretch receptors, it's got amino acids, it's got...

Erin Welsh

I thought coffee didn't have calories?

Erin Allmann Updyke

But it has stuff in there, right. It's not just like drinking water, right.

Erin Welsh

Right.

Erin Allmann Updyke

I don't know what else is in coffee.

Matt Candeias

Oils.

Erin Allmann Updyke

Oils.

Matt Candeias

Amino acids.

Erin Allmann Updyke

Amino acids. Other compounds that are going to stimulate your... Plus also you drink it with half and half Erin.

Erin Welsh

Sometimes.

Matt Candeias	It's also gotta be negligible because all the fasting, intermittent fasting stuff is like coffee's fine, don't worry about coffee.
Erin Allmann Updyke	Yeah, it's true. You wanna know a fun side note use of caffeine? I learned this while researching, I think it's fascinating. Caffeine is used in premature newborns to help prevent apnea. So to make them breathe better, essentially.
Matt Candeias	Wow.
Erin Allmann Updyke	Because it helps your diaphragm, it helps their diaphragm to be more active and prevent complications from not breathing properly. So not just caffeine but another... So caffeine is in a class of compounds called methylxanthines and there's another methylxanthine that we actually use to treat asthma called theophylline.
Erin Welsh	Interesting.
Erin Allmann Updyke	Yeah.
Matt Candeias	That's amazing.
Erin Allmann Updyke	I know.
Erin Welsh	So one of the things that I was always told growing up cause I loved coffee as a kid was that it would stunt my growth and then I grew up to be the shortest by far of everyone in my family.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so I've always wondered.
Matt Candeias	That's it.
Erin Allmann Updyke	That's it, Erin. No. It's just bad luck.
Erin Welsh	I like my height, excuse me.
Erin Allmann Updyke	Oh sorry.
Erin Welsh	Wow. (laughs)
Matt Candeias	Your genes are terrible and you have coffee to blame.
Erin Allmann Updyke	There's no association with short stature and caffeine intake.
Erin Welsh	Okay, what about any of the other studies? Has there been any association between caffeine intake and negative outcome in anything or any positive outcome?

Erin Allmann Updyke

So there's been a lot of talk about whether it has effects on your cardiovascular disease or increased risk of death from cardiovascular disease, there's not really an association there. There's some people that say it can increase your blood pressure which for someone who never drinks caffeine, if they drink caffeine you can see maybe like a 10 point bump in their blood pressure transiently. But if you drink caffeine regularly it has pretty negligible effects overall on your blood pressure. Basically all the things that we used to think caffeine is just so terrible, it has all these negative effects, it doesn't actually have a lot of association. A lot of the studies that used to show it, cause the problem with caffeine is that most of our studies about caffeine are coffee drinkers, right, which means they're dietary studies, which means they're really hard to do, there's a lot of different ways you can end up with biases like recall bias.

But then there's also a lot of interactions in terms of who drinks coffee. So in some cases it's actually people who are generally healthier that are drinking more coffee because they have access to it and they can afford it but on the flip side there's also associations with things like smoking and increased coffee drink, if you think about going out for a smoke break and a cup of coffee, etc. And so in the past a lot of studies have kind of confounded especially the effects of cigarette smoking and coffee drinking which is why for a while I think a lot of it was like, 'Coffee's terrible for you!' And then it was like, 'Coffee with save you!' And now it's kind of just like if coffee makes you feel more awake, then have some coffee.

Erin Welsh

What about the sleep impacts?

Erin Allmann Updyke

So caffeine increases your sleep latency which means it takes you longer to be able to fall asleep and subjectively people say that after drinking caffeine they feel less rested when they wake up, so they say that it interferes with their quality of their sleep. In terms of how long the effects of caffeine last in your body, it can vary quite a lot but on average the half-life is like 3-7 hours. So if you drink a cup of coffee in the morning, it should be well gone by the time you get to bedtime. But if you have a cup of coffee at like 4 in the afternoon, then yeah, you'll probably have still half of that in your bloodstream by the time you go to bed.

Erin Welsh

Okay.

Matt Candeias

Yeah, my cutoff is 3.

Erin Allmann Updyke

Yeah.

Erin Welsh

My cutoff is like 10am.

Matt Candeias

Oh geez.

Erin Allmann Updyke

I could chug like a triple espresso and fall asleep right after.

Matt Candeias

Med student.

Erin Allmann Updyke

And that's the thing, there is a lot of individual variation interesting he metabolism of caffeine. And then of course there's tolerance effects on top of all that.

Erin Welsh

I think it is interesting like there's still this association that we have with like, 'Oh I'm giving up caffeine,' it's like a very puritanical kind of glimpse of this thing that you know... Yeah, I don't know.

Matt Candeias

Yeah.

Erin Allmann Updyke

Yeah. Oh, another thing I'd like to say because I get this question a lot from friends. Caffeine and pregnancy. For a long time it was like no you can't have caffeine if you're pregnant. There's been really no good studies that show that small amounts of coffee, like up to 300 mg of caffeine which is about 2-3 cups depending on what size your cup is, doesn't really have any adverse effects on fetus or mom or anything. Yeah. However in the third trimester of pregnancy the half-life of caffeine is increased quite a lot longer which is super interesting and in newborns it's super long, like 80 hours it can be where that's the half-life for caffeine which is so interesting.

Matt Candeias

Oh wow.

Erin Allmann Updyke

Don't ask me why, livers, ooh man.

Erin Welsh

I also read that taking oral contraceptives increases the half-life of caffeine in the body.

Matt Candeias

Really?

Erin Allmann Updyke

It makes sense because caffeine is metabolized by your liver and oral contraceptives, especially ones with estrogen, are going to also have a lot of interactions with your liver and with the enzymes that potentially metabolize caffeine. So I don't know for sure but I wouldn't be surprised if that's why your half-life of caffeine increases in third trimester of pregnancy when your hormones are going wild.

Erin Welsh

Interesting.

Matt Candeias

That's wild.

Erin Welsh

That was cool.

Erin Allmann Updyke

That was fun guys, I'm glad you asked me so many questions because my notes were not organized but I feel like that was fun.

Erin Welsh

(laughs) I got overeager and I couldn't stop.

Matt Candeias

I'm learning. And what's amazing is how much of this I've just kind of taken with me and held on, like oh this is what caffeine does, never realized how on the fence at best some of this is.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. And I will say it's really, really difficult too because a lot of our data about caffeine comes from studies on coffee and coffee is not just caffeine, right. There is so many other compounds in coffee beans, there's so many other compounds in tea leaves that are different from coffee beans. So it is really difficult to fully get a handle on the exact effects of caffeine per se on these various processes. So Matt, can you please tell us why on earth would plants make such a substance and what is it good for IRL?

Matt Candeias

Amazing question, I'm so happy to be here to talk about this.

Erin Allmann Updyke

We'll take a quick break and then I want you to tell us all about it.

TPWKY

(transition theme)

Erin Allmann Updyke

All right Matt, hit us with the good stuff.

Erin Welsh

Yeah.

Matt Candeias

Yes. So yet another fascinating dive down the literature hole on this one and it was never as simple as I ever expected it to be so thank you again for forcing me to look at this, especially considering how dependent we'll say I am on this product. So as Erin established in the beginning, more than just coffee produces caffeine. I keep seeing this number around 60 different species tossed around but I did that whole web of science thing and traced it back and it's just something that someone threw out there, they cited like a vascular flora of the tropics and just kind of picked it out. And basically what we're gonna come down to here is that certainly far more plants than just 60 species do this but we generally only tend to look at things that interest or have a use to us in some way, so food, drink, medicine, caffeine, tea, chocolate, that sort of stuff. But again as we've established some of the most prominent ones are very familiar to us, so the genus *Coffea* which is the coffee plant and all of its relatives, *Theobroma* which is chocolate, *Citrus* actually produces a fair amount of caffeine, *Camellia* which is the genus for tea, *Cola* which is the genus for the cola tree which has gone on to give us a lot of soft drink flavoring. I see a hand raised here.

Erin Allmann Updyke

Yep, sorry. Does that mean like oranges have caffeine?

Matt Candeias

Not within the orange itself, we'll circle back to that though. But yes, yeah. All citrus do this on some level.

Erin Allmann Updyke

Wow, okay.

Matt Candeias

So Guaraná which is the genus *Paullinia* and you'll notice Guaraná is a common ingredient within a lot of energy drinks because there's other compounds related to caffeine that have stimulatory effects. And then a lot of hollies which if you've ever drank - you've both been in South America - yerba mate which comes from a holly. So there's again other stimulants in that but caffeine is a major component of it. And so those are just the ones that have economic use to us and that we study the most but again, this is something that's prevalent in a lot of different plant families and within those a lot of different species which is amazing. And the coolest part about it is that there is actually more than one way to synthesize caffeine if you're a plant. All of it involves alkaloid chemistry which caffeine is a type of alkaloid and it tends to rely on, as with any alkaloid production, high nitrogen in the soil. So you generally will find these sorts of species in rich soils because you need a lot of nitrogen to build alkaloids.

And that's kinda cool, you can look at something about the habitat that has allowed the evolution or at least selection to work on the evolution of these compounds. So the question then becomes why is it there? Nothing in nature is done wastefully, there's always some sort of function in there. Well it just so happens that researchers at the University of Buffalo which is my alma mater were studying the genus *Coffea* and they found that there are multiple genes involved in the synthesis of caffeine and that they did not arise all at once.

Erin Allmann Updyke

What?

Erin Welsh

What?

Matt Candeias

Yeah. So genes duplicate a lot in the plant world. It is not nearly as detrimental to have ploidy events in plants as it is in most animals I would assume, at least on the vertebrate spectrum of things. So ploidy is essentially a copying or duplication of the chromosomes, so you can have diploidy which means there's double the amount of chromosomes, triploidy, and so forth. And that's really common in plants and it's a very important way in which plants evolve and speciate and go about doing all the amazing chemistry that they do.

And within just coffee alone, the genus *Coffea*, the genes that are involved in the production of caffeine have duplicated multiple times throughout the history of this genus. And what's amazing is that in the creationist literature, the propaganda that goes out, they use this to say there's no way this could have happened because every step in the way is important, you can't have this irreducibly complex system without there being a creator. But when you actually look at every step, every gene duplication, every mutation that led to the process, every compound that is the end result of that has a function for the plant. It is always bitter and it's always stored in an area which will prevent herbivory.

Erin Allmann Updyke

I get so excited about things like this!

Matt Candeias

Every step of the way, every precursor compound is bitter and toxic to the exact kind of animals that want to nibble on these plants.

Erin Allmann Updyke

Oh my gosh.

Erin Welsh

It's beautiful.

Matt Candeias

It's mind blowing. And you look at these papers and you do see these chemical... I just like looking at them, I don't understand them to save my life but it is amazing that every one of these compounds, every step of the process has anti-herbivory function. Which brings us to the main function of caffeine for plants, the primary function or role that it's playing is as a defense against herbivory and pathogens which shouldn't surprise you, so many of the chemicals within the plant world that we like to utilize have their origins in keeping something from attacking or eating them. And so as Erin already mentioned, there's a lot of methylxanthines and the way that they've kind of come to this conclusion is that they're able to kind of turn these genes on or at least insert them into crop species like beets that don't normally produce caffeine. And every time they induce caffeine production in a crop species it has significantly less herbivory than their relatives, the clones that do not have caffeine production. Yeah.

Erin Welsh

So are they inserted in, like is that one of the strategies to create as a natural pesticide, GMO pesticide plant?

Matt Candeias

That is totally the motivation for doing this. I think the complication then becomes keeping it from being expressed in tissues you don't want it. So I don't want a beet that's gonna keep me up all night, right? So it's a cheap way to study this but in terms of the motivation behind a lot of these studies, it is trying to figure out how to get say foliar genes to express caffeine production as a quick and easy way because even at low concentrations that you would find in nature, these have a pesticidal effect which is pretty cool. Even at low doses it's keeping these things from being eaten.

Erin Allmann Updyke

Wow.

Erin Welsh

So caffeine is in so many different plant species all over the tropics naturally. So does that mean that it evolved separately or in these convergent evolution basically events? Is caffeine like a relatively simple molecule? Why caffeine? Why that one particular compound? You know what I mean? Do you know what I'm asking?

Matt Candeias

No, great question, yeah. And so yes, to answer your question it is independent evolution even if we just look at the families that we have listed already. Caffeine or coffee is in Rubiaceae, we have chocolate which is now Malvaceae, it's a mallow, we have the hollies which is Aquifoliaceae, they're their own family. You know, it's widespread and independent. In terms of the complexity, I think it's a pretty complex molecule and I think it's one of those things that just as evolution is working, as selection against herbivory works on it, you just have instances where it's either you just have some sort of byproduct where a mutation leads to it and it just happens to be more bitter and I think it's sort of selection against... Insects are really good at acclimating and evolving, this is that evolutionary arms race, this is why we have so many chemical pesticides within the plant community is just because insects are really good at adapting because their generation times are so low.

So I think it's a complex molecule and I think it's one of those things that just kind of gets refined depending on the selection pressures of that given environment and of course anything that's valuable to us and especially in terms of things that are tasty, we breed it to do way more than it normally would in the wild. Which I have really cool episode that's involving THC coming out soon which has similar conclusions in terms of our use vs natural background use.

Erin Welsh

Interesting.

Erin Allmann Updyke

Cool. Ooh, that sounds like a fun episode.

Matt Candeias

Yes. It is and I'm really excited for it. But yeah so at lower concentrations these methylxanthines as Erin already pointed out are really good pesticides and they activate something within the insects, which I actually wanted to ask Erin about, this is the adenylate cyclase. They activate that. They put that out there and were just like of course it does that. And I was like what does that mean?

Erin Allmann Updyke

Yeah, that's getting into the biochemistry of things that I am not gonna get into but the adenosine receptors, some of them increase cyclic AMP, some of them decrease cyclic AMP, so then caffeine... So it's all basically the same general compounds that it's going to effect in insects vs humans and other mammals if that makes sense, like on a biomolecular level it's the same basic stuff.

Matt Candeias

Yeah. Cool.

Erin Allmann Updyke

Yeah.

Matt Candeias

So apparently it works that way. (laughs) But again, plants have many ways in which they can defend themselves and there's mechanical defenses which are the thorns and spines, you grab a rose, you pay for it royally. But it's also just having tough tissues. And what's cool is in early development of leaves and stems and stuff, caffeine production is super high but as the leaves mature and become more tough, they kind of reinforce their cell membranes, caffeine production actually goes down which is why actually younger tea leaves are preferred, they have a higher... Because they're softer and more vulnerable they need the chemical defenses before they can beef up their structural defenses which if you think in terms of investment in defenses, making lots of chemicals is expensive whereas just using and reinforcing, that lasts a lot longer which is really cool.



Erin Allmann Updyke

Oh that's so cool!

Erin Welsh

That's really amazing.

Erin Allmann Updyke

Wow.

Matt Candeias

Yeah. Okay so caffeine is in the seedlings really early on because again it's like those mechanical defenses, the seeds are small, they're really vulnerable to herbivores, smaller stuff especially like slugs and everything that wants to eat a small, tender seedling. So caffeine production for about the first 8 weeks is super, super high and then it eventually starts to decline just like we see in leaves throughout the germination process. So as long as the seeds are small and have this uniform soft tissue, this accumulation of caffeine is just going to continue to increase which is pretty amazing. But as soon as the seeds start to toughen up, that's when you start to see that decline which again goes back to this idea that nothing is being done in a sort of a wasteful sense in that a lot of these productions of chemicals, any chemical compound within a plant, it can either be inducible or it's really during a short period of time of development because they're not doing this for us, they're not doing it because we want them to, they're doing it to protect themselves.

And within plants like tea, there's also a shift you'll see in sort of where the caffeine's being stored. So once those tea leaves really start to toughen up, they start really packing it into their vacuoles which whenever an insect bites into it those burst and that gets into their mouth and that's where you start to see again that sort of protection effect where it's just like, 'Ugh god, this is disgusting, I gotta stop eating it.' But they also put it into their vascular bundles which is the vascular tissue throughout the plant and that's one of the main conduits by which pathogenic fungi will attack and any organic gardener knows that a lot of antimicrobial properties are within coffee grounds as long as you haven't boiled them. And so there's also a big component of keeping microbial pathogens away. So it's not just herbivory, it's protecting against fungal attacks as well. But that's cool because it's also kind of funneling it to the areas of the plant that are most vulnerable.

Erin Allmann Updyke

Oh my gosh.

Erin Welsh

That's super cool.

Erin Allmann Updyke

Plants are so smart.

Matt Candeias

Yeah.

Erin Welsh

So if the caffeine molecules act on insects in similar ways as they do on humans, why - and I don't know who I'm directing this question towards or whom I'm directing this question towards - but why do humans become dependent and want more caffeine and insects are like ugh? Because I mean obviously we like the bitterness and there is obviously a bitter taste and it's evolutionarily wise I'll say just for lack of vocabulary at this point in the day to avoid the taste of bitter things cause it tends to be poisonous or toxic. But are there insects or animals in general that like caffeine?

Matt Candeias

That's a really good question. So for instance if this was alcohol I would say yeah, there's tons of evidence that animals are seeking it out and having similar issues with alcohol that even humans have, for caffeine I don't know, I don't think so although there is this evidence that we talked about the civets having to pass the beans and making the best cup of coffee. So I would say potentially but that's a mammal with a larger body mass, I would assume for as anxiety-ridden as I can be after 2 or 3 cups of coffee, a few bites on a leaf for an insect is probably really rough for that body mass.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah. And I don't wanna say like that the effects of caffeine are the same in an insect as they are in a human, I just mean on a molecular level the changes are probably gonna be similar.

Erin Welsh

Right

Matt Candeias

Right.

Erin Welsh

The mechanism of effect.

Erin Allmann Updyke

Right, yeah. But it's a really interesting question.

Matt Candeias

Yeah I would be really curious to look at even just dispersal cause you have to figure those coffee seeds have to go somewhere, right, and dispersal is usually especially if it's a red berry aided by some sort of animal. And so I wonder if caffeine which I'll actually get to in a little bit here some other ways that maybe caffeine could work for animals and plants together. But first I wanna talk to you about competition. Because everyone thinks about plants as sort of these static, not really interacting with the world kind of organisms and especially not harming each other or working against each other, you know the world wide web stuff came out, kumbaya, everything's getting along. Well actually plants are competing all the time, that's the only reason we have tall plants at all is because they can shade each other out, they take up space where other roots could go, they're competing for nutrients, water, all that sort of stuff. And so it makes sense that at some point anti-competition mechanisms would evolve in some species and there is a lot of evidence that caffeine can be involved in anti-competition interactions among especially young plants.

Erin Allmann Updyke

What?

Matt Candeias

So they looked at putting coffee seeds into auger just to see what was going on with relative caffeine levels as plants germinate and grow and we already established that they will really ramp up production while the seedling itself is growing. But what they found out is that the seed coat will actually leach a considerable amount of caffeine, up to 22% of the caffeine within the coat itself into its surrounding environment. And when they use different levels of caffeine, especially that reflect background natural levels of what we're seeing from the leaching of the seeds, it's actually been shown to inhibit germination and growth of the surrounding vegetation.

Erin Allmann Updyke

What?

Erin Welsh

How?!

Matt Candeias

Yeah. So these seedlings are releasing a ton of caffeine into the soil which will inhibit the germination of potential competitors that could overgrow them and steal light, water, and nutrients from them. So caffeine is actually also an anti-competition compound. It's allelopathy, it's using chemical warfare.

Erin Welsh

How is it doing it?

Matt Candeias

I do not know the mechanisms of it but I'm assuming it has something to do with the metabolism. Here's a plant that's producing it, harming other plants that might not be or it could even just be within its own self, within its tissues it's fine but if it's in the soil interacting with the root hairs, maybe even the fungi that they're partnering with, there's a lot of mechanisms with which allelopathy could work and it's one of those areas of science that we're only really starting to get our heads wrapped around and it's difficult to study. So there's a lot of open ended questions but that's just a call for more attention, call for more work. Coffee's really easy to germinate so that's something you could do in a greenhouse study pretty much anywhere in the world. So hey, kids.

Erin Allmann Updyke

Hey! Science experiment!

Matt Candeias

So what's amazing is we have this dual benefit here. We have an anti-herbivory, antipathogen really protecting plants as they grow and then they're also involved in anti-competition, so keeping your space free of potential competitors. But going back to the question about citrus, there is also evidence that caffeine is highly involved for a lot of the plant species that produce it in pollination. And this is where things get really cool.

Erin Allmann Updyke

Stop it.

Erin Welsh

Yeah.

Matt Candeias

Yeah. So this is best studied in coffee and citrus but again with the amount of plant species that are known to do it and probably are still yet to be described or discovered to be doing it, a lot of these plants pump small amounts of caffeine into their nectar. Small amounts, not nearly enough to be at that level of sort of anti-herbivory or preventative. But when they looked at this they started asking these questions, what is this anti-herbivory compound doing in nectar? This is supposed to be the one place where a plant really wants and organism or at least an insect to interact with it. So they studied this in honeybees. And again all of this is done in species that have been domesticated, have a use to humans just because of the funding, but it really has a lot of implications for what's going on out in the wild. Nonetheless, caffeine concentrations in nectar were found to not exceed the bee's bitter taste threshold and I really wanna know how they decided where that was.

Erin Allmann Updyke

(laughs) They just asked, they were like, 'Can you taste it now?' And the bees were like, 'Buzz!' And they were like, 'Can you taste it now?' And they were like, 'Buzz, buzz!'

Matt Candeias

And then they were like, 'Buzz, buzz.' But the fact that the levels in the leaves and the levels in the nectar seemed to be highly regulated for uptick in production but keeping below a threshold in the nectar implies that there is some sort of selection for pharmacological activity within the nectar that isn't supposed to function as a repellent.

Erin Allmann Updyke

Right.

Matt Candeias: And what they found is that when researchers presented bees with naturalistic levels of caffeine in any sort of drink, the bees were able to not only remember, locate, and understand the floral scents much higher than in any situation in which there was no caffeine in the nectar.

Erin Allmann Updyke: So it also increased their alertness and their productivity, etc.

Erin Welsh: And their focus and their desire to poop - no.

Erin Allmann Updyke: Their focus. (laughs)

Matt Candeias: Yep, they're just squirting little bee poops everywhere as they go. But the thought is that actually the plants have also co-opted a slight amount of caffeine in their nectar to enhance the memories of reward within their pollinators which secures pollinator fidelity and improves the reproductive success of the plant overall.

Erin Welsh: That is incredible.

Erin Allmann Updyke: That is beautiful.

Matt Candeias: It's mind blowing. So you have defense, you have minimizing competition, and you've got your sex taken care of. This is hitting all three of the major instances of things that actually influence plants in all steps of their life, some of the most basic things in life is surviving, not getting sick, and being able to reproduce and caffeine is involved apparently in all of those in the species that are producing it.

Erin Welsh: Wow.

Erin Allmann Updyke: Wow. What a gorgeous story.

Erin Welsh: Did you come across anywhere about when it was estimated that caffeine first evolved, like when plants first started to produce caffeine?

Matt Candeias: So I did but it seems like one of those things that's heavily debated because you do have gymnosperms that produce like ephedrine if from ephedra which is gymnosperm that's probably much older than most of the flowering plant lineages and estimates put most conservative the evolution of flowering plants somewhere in the Cretaceous, so when T. rex was roaming the landscape. And so some of these lineages can be dated back to the Miocene, the Eocene, so 40-50 million years ago but some of these lineages go back much farther, there's fossil evidence for them. And the problem is we just don't know, you can't look at a fossil and tell what kind of chemical constituents were being produced, all we can say is this is affiliated with this order, this order's known for producing a lot of it, potentially it was there.

Erin Allmann Updyke: Yeah, yeah.

Erin Welsh: And are all of these plant species concentrated in the tropics and subtropics?

Matt Candeias

So the major ones that we talked about today, yes. And there is a really interesting latitudinal gradient for anyone that's familiar with this, it's basically going from the poles to the equator. There's usually a really strong gradient of spices, all of these antimicrobial, anti-herbivory compounds, they increase the closer you get to the equator but so does biodiversity. So all of the pressures and the climate of inducing microbial attacks, fungal attacks, those are all way worse in the tropics. So the idea that you would see a lot more plants potentially stumbling onto this evolutionary process in the tropics, it just makes biological sense in the long run or the laws of thermodynamics probably play in there just as much as evolution does.

Erin Welsh

Oh my god.

Matt Candeias

Yeah.

Erin Welsh

Ugh, I love these episodes.

Erin Allmann Updyke

I was just gonna say that! I love these episodes so much.

Matt Candeias

I know. These are the horizon-expanding episodes for me cause it's like I'm able to connect so many more dots afterwards.

Erin Allmann Updyke

Yeah!

Erin Welsh

It's so cool, it's so cool.

Erin Allmann Updyke

Oh my gosh. Wow. Plants are really incredible, we don't give them enough credit.

Matt Candeias

I'm telling ya. That's why I'm here.

Erin Allmann Updyke

That's why we need you. That was so fun, thank you so much. I learned...oh my gosh.

Matt Candeias

Oh my gosh, yeah, thank you.

Erin Welsh

This was so great. Yes, thank you.

Matt Candeias

I always walk away a more full person after this, thank you very much.

Erin Welsh

(laughs) This was great.

Matt Candeias

Yeah it was.

Erin Welsh

Now we just have to brainstorm our next one.

Erin Allmann Updyke

Oh my gosh, yeah.

Erin Welsh

Any requests anyone? Send them our way.

Matt Candeias

Yeah, please.

Erin Welsh

I guess do we do sources now?

Erin Allmann Updyke

We should do sources, yeah.

Erin Welsh

Okay. So let me pull mine up. I drew heavily from a few different books that I'll mention. One was called 'The World of Caffeine: The Science and Culture of the World's Most Popular Drug' by Weinberg and Bealer. And then I also listened to a book cause it's only an audiobook which is the first time I've encountered that called 'Caffeine: How Caffeine Created the Modern World' by Michael Pollan. And then finally by Mair and Hoh, 'The True History of Tea'. And I watched a documentary that is on YouTube called Black Coffee and it's a Canadian National Film Board documentary, it's like a three-parter, it's really interesting but I will say that the last section is a bit too much like a Starbucks episode for me to feel comfortable with. But the first two are great.

Matt Candeias

Cool. So yeah, I pulled from a handful of papers that I guess we can link in the show notes or whatever you like to do. So the first one was 'Caffeine and related methylxanthines, possible natural occurring pesticides' by Nathanson 1984. The second one was 'Purine alkaloid formation in buds and developing leaflets of Coffee arabica, expression of an optimal defense strategy' by Frischknecht et al 1986. 'Conversion evolution of caffeine in plants by co-option of exapted ancestral enzymes' by Huang et al 2016. And 'The immunohistochemical localization of caffeine in young Camellia sinensis' by Breda et al 2013. And the finally 'Caffeine in floral nectar enhances a pollinator's memory of reward' by Wright et al 2013.

Erin Welsh

Awesome.

Erin Allmann Updyke

Excellent. I had a number of articles, I don't want to read all of their titles so suffice to say we will post them all on our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com) where you can find our sources for this episode and every single one of our episodes. There's some great ones especially if you wanna learn more about for example the effects on dementia, whether or not it's a diuretic, the effects on your cardiovascular health, etc etc. I got papers for all those.

Erin Welsh

And we'll also put all of these onto our [bookshop.org](http://bookshop.org) affiliate page as well as our Goodreads book list. So if you want to read some books or listen to some books, check them out.

Erin Allmann Updyke

Well thank you again Matt so much for coming on, we love having you on this podcast, it's so much fun and we learn so much every episode.

Matt Candeias

Thank you both so much for having me, it's always a blast, I miss you all so much and I can't wait til we can do this in person again.

Erin Allmann Updyke

I know.

Erin Welsh

Oh my gosh, I know. I know. I was just thinking that and I was like I can't even say it, it's too sad.

Matt Candeias

I know. Sorry, I'm the downer.

Erin Welsh

Well hey, usually I'm the downer so it works. And then when we do meet we'll drink all the quarantinis, we'll just carry on and then have some caffeine for the next morning.

Matt Candeias

I was gonna say quarantinis and coffee, we'll be set.

Erin Welsh

Quarantinis and coffee!

Erin Allmann Updyke: It's a bad combo by the way but that's a separate topic.

Erin Welsh: You mean Four Loko's bad for you?

Erin Allmann Updyke: Yep. Yeah.

Matt Candeias: What? Oh my god.

Erin Welsh: Also thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Allmann Updyke: And thank you to you, listeners! We hope that you enjoyed this episode, thanks so much for sticking around.

Erin Welsh: Yes, thank you, thank you.

Matt Candeias: Yeah, thanks for listening.

Erin Welsh: Wait Matt, you should tell everyone where to listen to your stuff and where to find stuff.

Matt Candeias: Yeah. In Defense of Plants is on all the major podcatchers, just google it, so you know iTunes, Spotify, Stitcher, that sort of stuff. Indefenseofplants.com is the website, blog, a lot of really cool updates, that's where you're gonna find them. Twitter, Instagram, please follow there, I've got a lot of cool stuff coming out in the next couple of months, some big announcements. So please stay tuned if you enjoy these sorts of things, there's more to be found. So yeah, go check it out and say hi.

Erin Welsh: Yes, yes, yes.

Erin Allmann Updyke: Excellent.

Erin Welsh: Yeah. I can attest that the In Defense of Plants Instagram is incredible.

Matt Candeias: Oh thank you. I enjoy it, I appreciate that.

Erin Welsh: It's so great, great content. Okay well until next time, wash your hands.

Erin Allmann Updyke: You filthy animals!