KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

HPA-D 3-5 – Part 10

Licorice is another botanical frequently used to treat HPA-D.

The active compound in licorice is glycyrrhizin, and it has a very similar structure to corticosteroids. Its metabolites have been shown to block 11-β HSD2, which is the enzyme that converts cortisol to cortisone. This results in increased levels of circulating cortisol, especially in the tissues that are attempting to block cortisol binding to mineralocorticoid receptors. This is why chronic high intake of licorice is documented to raise blood pressure through cortisol binding of mineralocorticoid receptors in the kidneys. This causes a pseudoaldosteronism condition where you see increased water retention and blood volume leading to hypertension, but note that this only happens in people with normal or elevated cortisol. It's not going to happen in someone with low cortisol. This is one reason why I really prefer the DUTCH test because, as we've seen, even someone who has low free cortisol, if they have very high metabolized cortisol, you may want to think twice about using licorice for that person, or at the very least, you'd want to monitor their blood pressure closely if you do use it.

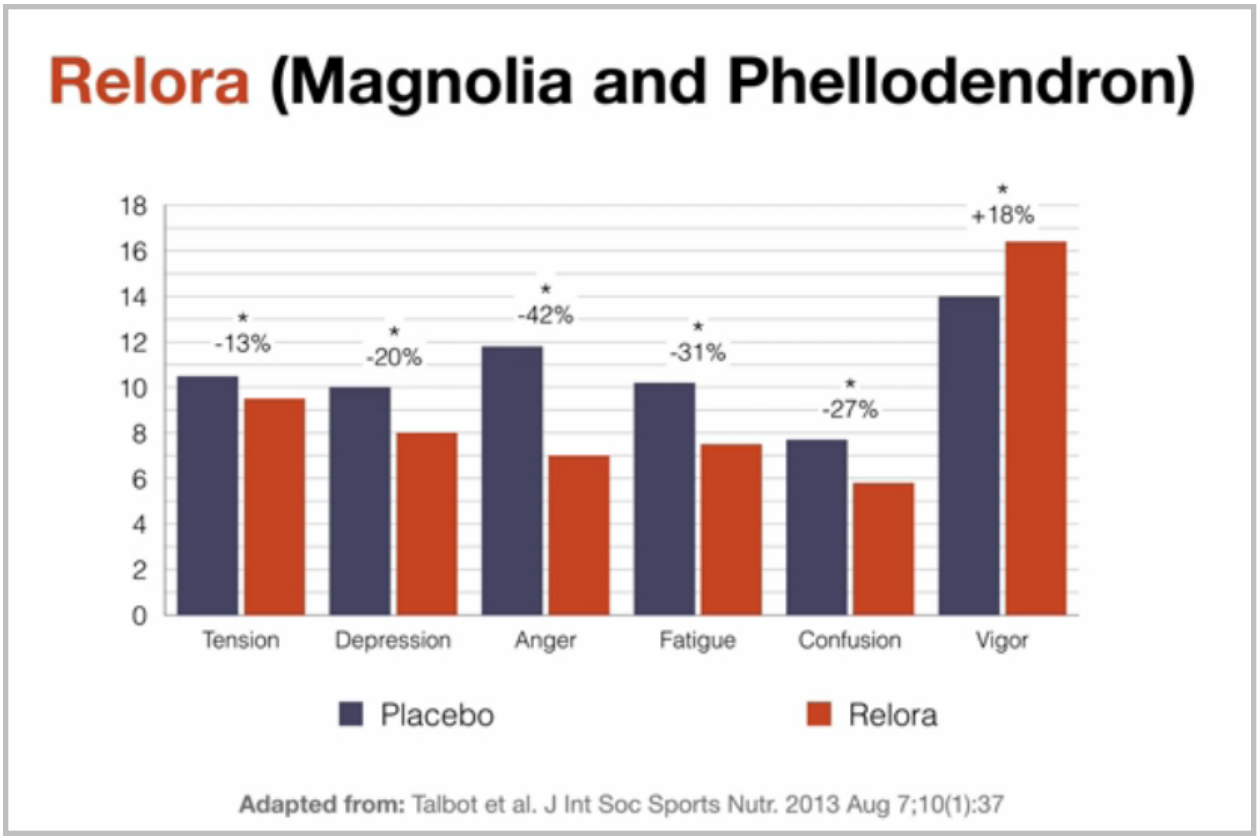
In people with low cortisol, licorice used in appropriate doses can be helpful in maintaining adequate cortisol levels. As I explained on the last slide, it doesn't actually raise or increase cortisol production, but it increases the circulating half-life of cortisol, which ends up having a similar effect. For example, licorice extracts have been historically used to treat Addison's disease, but you have to be aware of the benefits versus the risks.

The European scientific organizations have cautioned against consuming more than 100 mg per day of glycyrrhizin. Dose-response studies have found that glycyrrhizin triggers mineralocorticoid receptor-like side effects between 215 and 270 mg per day, so the upper threshold of 100 mg is probably overly conservative, but it is safe. Women appear more vulnerable than men to these side effects. Some studies suggest an individual's microbiome profile may actually affect their susceptibility to those side effects, which is interesting. Licorice is contraindicated with high blood pressure, blood sugar medication, corticosteroid use, insulin, laxatives, oral contraceptives, and digoxin.

The good news is you don't need very high doses of glycyrrhizin or licorice to show benefit. Studies have shown that the very safe upper limit for glycyrrhizin is 0.23 mg/kg per day for all people, including people with higher cortisol. If you imagine a 75-kilogram person, 165 pounds, he could consume 17 mg per day long term of glycyrrhizin and not experience any side effects.

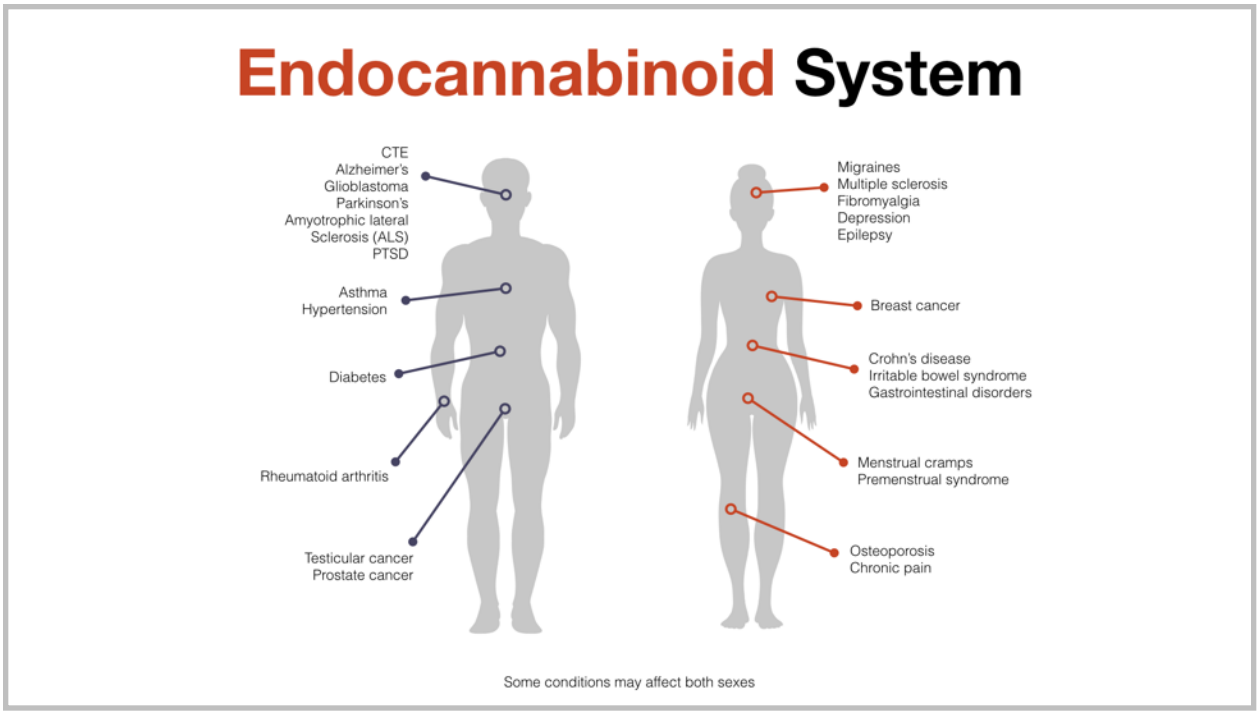
Licorice powders are usually 10 to 20 percent glycyrrhizin. Liquid extracts are typically 1:1 or 1:2 extracts, that is, one part licorice to one part alcohol and not standardized to glycyrrhizin content, although some liquid extract producers claim that there is 0.5 to 0.75 mg of glycyrrhizin per drop of the tincture. That said, I still recommend avoiding licorice in people with very high cortisol, or at least staying well below that 17 mg per day of glycyrrhizin limit. You can use it in patients with low cortisol, especially those with a high ratio of cortisone to cortisol because licorice would reduce the conversion of cortisol to cortisone, so that is one of the particular use cases for licorice. Note that some research suggests that licorice reduces the sulfation of DHEA to DHEA-S, and that allows more conversion of DHEA to testosterone.

The next botanicals to discuss are Magnolia officinalis and Phellodendron amurense. These have, again, a long history of use in traditional Chinese medicine to relieve stress and stress-induced symptoms. Magnolia officinalis has been found to decrease cortisol. It is one of the other few natural substances along with phosphatidylserine and GABA that has been shown to do that. It is most well known for its anti-inflammatory and calming properties.



Magnolia and phellodendron are combined in a product called Relora, which has shown benefits in clinical studies. According to a randomized, double-blind, placebo-controlled trial of Relora, participants experienced an 11 percent decrease in overall stress, 13 percent decrease in tension, 20 percent decrease in depression, and 42 percent decrease in anger when compared to placebo, and I've put a chart here illustrating those results on the slide. Relora has been shown to reduce sleep latency, increase overall well-being, and prevent weight gain by reducing cortisol that contributes to belly fat. The dose of Relora is typically 500 mg a day taken in two divided doses, though up to 750 mg per day has been shown to be safe for shorter durations of a few weeks or months.

The last botanical compound I want to discuss is cannabidiol. Cannabidiol, or CBD, is one of the 85 active compounds found in the marijuana plant, cannabis. Unlike THC, the active compound in cannabis known for its psychoactive properties, however, CBD is not psychoactive. It doesn't produce a feeling of being high, and it can actually counteract that feeling. CBD has been studied extensively over the past few years and has a number of medicinal properties that could help to reverse HPA-D. In fact, it addresses all four primary triggers of HPA-D: perceived stress, inflammation, dysglycemia, and circadian disruption.



Research on anxiety, stress, and fear is focused almost exclusively on the role of certain neurotransmitters called monoamines, but recent studies have begun to highlight other neurochemical systems, including cytokines, peptides, and bioactive lipids, in particular the role of the endocannabinoid, or ECS system, in stress and fear responses. The ECS is a complex physiological network within the human body comprising cannabinoid receptors, CB1, and CB2. Cannabinoid receptors and the biochemical machinery necessary to synthesize and generate cannabinoids are present within areas of the brain that are known to control emotional behavior, mood, stress, and fear. Studies have shown the activation of cannabinoid receptors within the brain reduces panic and anxiety behavior or the fight-or-flight reaction. This appears to be dose and compound dependent, so if there is too high of a dose, or if the dose contains more THC than CBD, and THC being psychoactive, it can actually amplify fear and anxiety, which explains why some people get paranoid when they take too much THC.

A randomized, double-blind, placebo-controlled trial on 15 humans demonstrated up to 600 mg of CBD reduced measured anxiety. Another study found that CBD promoted neurogenesis in the brain. It led to the formation of new neurons in the hippocampus, which is typically associated with conscious memory and navigation. Other research on neurogenesis has shown that it helps to regulate stress levels, and this may be another mechanism by which CBD has anti-stress effects.

CBD is also anti-inflammatory. CB1 and CB2 receptors have been found on immune cells, which suggests that cannabinoids play an important role in the regulation of the immune system. Recent studies have demonstrated that the administration of THC into mice triggers marked apoptosis in T cells and dendritic cells resulting in immunosuppression. Several studies showed that cannabinoids

downregulate cytokine and chemokine production and, in some models, upregulate T-regulatory cells as a mechanism to suppress inflammatory responses.

CBD has been shown to be effective for numerous conditions characterized by inflammation, including IBD, chronic pain, multiple sclerosis, liver disease, rheumatoid arthritis, cancer, allergic asthma, autoimmune retinitis, and type 1 diabetes.

The endocannabinoid system participates in the control of lipid and glucose metabolism at several levels, with the possible endpoint of the accumulation of energy as fat. The cannabinoid receptors are deeply involved in all aspects of the control of energy balance in mammals. CBD has been shown to lower the incidence of diabetes in nonobese diabetic mice and arrest the onset of autoimmune diabetes in mice. In humans, marijuana and CBD are associated with lower levels of fasting insulin and HOMA-IR and smaller waist circumference. This might be counterintuitive, since many people who use marijuana get the munchies, but CBD doesn't tend to have as strong an appetite-stimulating effect.

CBD has mistakenly been described as sedating. However, in modest doses, CBD is actually mildly alerting. Cannabidiol activates the same adenosine receptors as caffeine, which is obviously a stimulant. That said, studies in rats have shown that CBD increases total sleep time and sleep latency during the light period of the day. It regulates sleep stability and helps reset the circadian clock.

Also, several patients with sleep issues have reported that ingesting a CBD-rich tincture or extract a few hours before bedtime, not right before bedtime but a few hours before, has a balancing effect that facilitates a good night's sleep. In my clinical experience, that is exactly what happens with CBD. If it is taken too close to bed, it can actually delay sleep onset, but if it is taken around dinnertime or in the late afternoon, it can have a really calming effect and improve sleep quality, possibly because of its anti-inflammatory effects in a lot of patients.