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Coronavirus, ACE2 receptor, and Crataegus

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After the 2002 SARS-coronavirus outbreak, it was discovered that the virus uses the human cell-receptor ACE2 in order to enter the cell. In March, some of the Chinese researchers who made this initial discovery published basic science showing that the COVID-19 virus, closely related to the SARS virus, uses the same receptor to infect the cells (Wan et al.). This receptor, part of the renin-angiotensin hormonal system which helps to regulate blood pressure and other functions in mammals. The SARS virus and COVID-19 evolved in bats, which share this receptor. ACE2 is present on parts of the lung and respiratory tract, in the digestive tract, and several other tissues. The lung and digestive tissues help explain the symptoms of the disease which may be primarily respiratory, digestive, or both.

A speculative article on whether patients on several drugs, including Ibuprofen, which are known to increase ACE2 expression on cells, could more easily develop infection or progress to more severe disease. The issue is that in response to the drugs, the number of ACE2 receptors can increase, either acutely or with chronic use (Fang et al.). The article, which is theoretical, has received intensive criticism, based on the complexity of the ACE2 and its interaction with the hormones and the ACE1 receptor, and a dual pathway where inhibiting ACE with drugs might lead to either an inflammatory or an anti-inflammatory response. Some front line clinicians are paying attention however. And the continuously updated online *Internet Book of Critical Care (IBCC),* in its chapter on chapter on COVID-19 advises critical care physicians to avoid all non-steroidal anti-inflammatory drugs (NSAID) because of their potential to up regulate the receptor and worsen the infection. They may also cause kidney toxicity, with kidney complications common in serious COVIC-19 infection. https://emcrit.org/ibcc/COVID19/ The issue of other medications that affect ACE2 to discussed at length in the IBCC, and concludes that more questions than answers remain on the subject.

Speculation is now raised among herbalists in discussion lists and social media about whether *Crataegus* should be avoided in possible COVID-19 patient because of its reputed effects as an ACE inhibitor. This concern can be quickly disposed of because, clinically, Crataegus does *not* act as an ACE inhibitor. Any information on this subject comes from lab dish and animal trials, and should thus be rejected out of hand until actual human clinical effects are demonstrated. Nevertheless I will describe the research in more detail to demonstrate how extrapolation of how pre-clinical in-vitro and in-vivo research is fundamentally flawed. The original information about possible ACE-inhibiting effects of *Crataegus* came in 2001 in research looking for plant constituents with ACEi effects. Constituents from *Crataegus* were extracted through a complex process and then tested in lab experiments with ACE derived from rabbit lung tissue. Some *Crataegus* flavonoids and procyanidins had an effect in this experiment. This cannot be extrapolated to the oral use of Crataegus in living human subjects. The concentration of constituents used was 0.33 mg/mL, a concentration which would be impossible to obtain in the human serum with any route of administration for Crataegus (Lacaille-Dubois et al.) In 2013, other researchers found ACE-inhibiting effects, again, in lab research. As with the previous research, the form and concentration used in the study would be impossible in the human living system (Sharifi et al.) In 2019, Iranian researchers found that a water extract of a *Crataegus* species had an effect on the same order of magnitude as a standard ACE inhibitor drug in an animal trial, but the dose required was 300 mg/Kg given intravenously. For comparison, in a 75 kg adult human would require a dose of 22.5 grams of Crataegus, intravenously, biologically impractical if not impossible (Younis et al). Trials that have tested concentrated extracts of Crataegus in actual hypertensive patients have found either no effect, or a slight effect – a drop of about 2 points in diastolic pressure after 12 weeks (Walker

et al.) *Crataegus* cannot be acting as an effective ACE inhibitor in humans if it cannot lower blood pressure even after several months of high-dose administration.

One way to clarify or determine the effects of herbs is through accidental overdose, and I have one anecdote demonstrating the mildness of *Crataegus* as an herb, with low potential to create side effects. My teacher Cascade Anderson-Geller related that she had a patient who she wanted to take *Crataegus*, but he had limited means. So she tinctured him a pint of *Crataegus* in brandy and gave it to him. She was unaware that this man was alcoholic, and he went home and drank the entire pint in an evening. She said he felt no ill effects from it, no symptoms of hypotension. If Crataegus were an effective ACE inhibitor in the doses that herbalists typically dispense it, or even if it were a very effective hypotensive herb at all, the man would have certainly felt something by drinking a pint.

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