Is Licorice anti-viral?

By Paul Bergner

Win an emerging workdwide COVID-19 pandemic, we are of course interested in herbal prevention or treatment. I am seeing various memes about *Glycyrrhiza* being anti-viral, and specifically against the previous SARS coronavirus. I am not a nay-sayer about anything herbal, and *Glycyrrhiza* may be useful in any respiratory condition, through demulcent, expectorant, tonic, or other effects. But we don't find traditional use for viral infection. If a statement is to be made based on scientific research, rather than on historical or empirical information, then some critical thinking about that scientific research is in order. Of concern is that with persistent or excessive use of licorice for supposed antiviral properties, its traditional indications, contraindications, and its well-known side effects may be forgotten.

The research on the antiviral properties of Licorice have been nearly exclusively on the constituent *glycyrrhizin.* This research has been in lab dish viral cultures, intraperitoneal injection in animals, and (mostly) intravenous administration to humans. Intravenous administration of purified glycyrrhizin is a standard medical treatment for viral hepatitis patients in Japan. In all such cases, glycyrrhizin must come into contact with the virally infected cells or the immune system of the host at a concentration sufficient to have an effect. But pharmacokinetic studies comparing intravenous glycyrrhizin versus oral glycyrrhizin or oral whole licorice root show that virtually no glycyrrhizin enters the plasma when taken by the oral route, and in comparison, only extremely small quantities of its metabolite *glycyrrhetic acid.*

In the accompanying graph, the bottom three curves show the levels of glycyrrhizin in the plasma after IV administration after conventional doses. The highest levels are from about 12-40 micrograms/mL of plasma over 12 hours. These are the levels found to be antiviral and used for this purpose in Japan. With oral use, however, *no* glycyrrhizin is detected in the plasma, but rather its metabolite glycyrrhetic acid is found, as in the top graphs for the three subjects, but at levels not exceeding 0.2 micrograms/mL, or between 1/60th and 1/200th of glycyrrhizin concentrations found with IV administration. When taken orally, glycyrrhizin is metabolized by the gut bacteria and the liver to produce this glycyrrhetic acid and several other metabolites, and glycyrrhizin itself does not enter the plasma. The effect of these metabolites on viral infection is not known. We do know that when glycyrrhizin is given by IV, these bio-transformations do *not* occur, these metabolites are not detected without a first-pass through the gut. So any antiviral effect of IV glycyrrhizin is due to the glycyrrhizin itself and not these metabolites. The oral administration is not the equivalent of intravenous use either for constituents in the plasma or their levels.

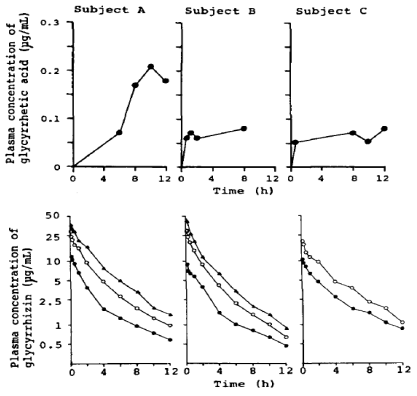

Figure 2—(Top) Plasma concentration–time profiles of **2** after oral administration of **1** (100 mg) to three subjects. **(Bottom)** Plasma concentration–time profiles of **1** after intravenous administration of **1** at different doses to three subjects. Key: (●) 40 mg; (○) 80 mg; (▲) 120 mg.

With oral administration of Glycyrrhiza root, at a dose of glycyrrhizin approximating that in the study above, the plasma levels of glycyrrhetic acid achieved are about the same. In the trial above, the glycyrrhizin dose was 100 mg. In this trial, first a glycyrrhizin dose sixteen times higher (1.6 grams) was given. See the upper curve in the two graphs at the right. The metabolite glycyrrhetic acid did not rise above 2.5 micrograms/mL in either patient even with this extremely large dose. The lower curve in each graph reflects serum glycyrrhetic acid in plasma after an *oral* dose of 21 grams of *whole licorice root*. This dose may contain about 100mg of glycyrrhizin based on average content of the root. In this case the serum levels remain below 1 microgram/mL. Note that this dose is much higher than the 2-12 grams daily dose recommended in Chinese medicine, and is not practical clinically. The authors speculate that a reduced absorption of glycyrrhizin from whole root compared to the purified form when taken orally is responsible for the lower levels of the metabolite.

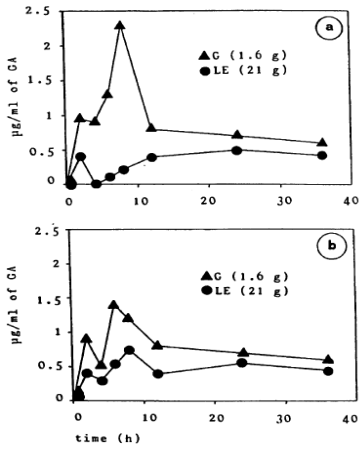

Figure 5. Plasma levels of glycyrrhetic acid (GA) after oral administration of glycyrrhizin (G) or aqueous licorice root extract (LE) in male (*a*) and female (*b*) volunteers.

Of concern, then are the possible side effects of taking licorice persistently or in higher doses for supposed antiviral effects. Traditionally Glycyrrhiza can be problematic in acute ailments, in conditions of “dampness,” and with patterns of excess, and even small doses can manifest these problems within a few days. Conventionally, persistent use can cause headache, water retention, hypertension, electrolyte imbalance, and we have some indication that it lowers testosterone levels in males and females.

Yamamura Y, Kawakami J, Santa T, Kotaki H, Uchino K, Sawada Y, Tanaka N, Iga T. Pharmacokinetic profile of glycyrrhizin in healthy volunteers by a new high-performance liquid chromatographic method. J Pharm Sci. 1992 Oct;81(10):1042-6.

Cantelli-Forti G, Maffei F, Hrelia P, Bugamelli F, Bernardi M, D'Intino P, Maranesi M, Raggi MA. Interaction of licorice on glycyrrhizin pharmacokinetics. Environ Health Perspect. 1994 Nov;102 Suppl 9:65-8.