

# Drugs That Interfere With Herbs

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## Abstract

Although research is scanty on herb–drug interactions, there are indications that prescription drugs can significantly affect the efficacy of botanical medicines used to treat many conditions successfully. This article reviews that research and suggests that, when considering herb–drug interactions we need to determine not only if herbs affect drugs' actions adversely but also the extent to which drugs affect the medicinal action of botanicals adversely. Coverage includes antibiotics and glycosides; *Glycyrrhiza uralensis* (licorice) and the antibiotics amoxicillin and metronidazole; *Glycine max* (soy) and antibiotics; *Actaea racemosa* (black cohosh) root and tamoxifen; and botanicals and antiacid drugs.

## Introduction

Concern has been raised about the potential of herbs to interfere with drugs, as exemplified by the recognition that *Hypericum perforatum* (St. John's wort) can decrease systemic levels of many drugs significantly in the body, apparently through induction of CYP3A4.<sup>1</sup> However, an equally relevant question is whether drugs might interfere with the actions of herbs. Though far less work has been done on answering this question, there are hints that drugs can sometimes block the efficacy of herbs. Such interactions should be investigated further and publicized so that patients and practitioners can make informed decisions about whether to take drugs that might block herbal medicines from working.

## Antibiotics and Glycosides

Glycosides in herbs are normally metabolized by colon microbes, releasing aglycones for absorption and systemic activity, as exemplified by glycyrrhetic acid from *Glycyrrhiza glabra* (licorice).<sup>2</sup> These aglycones may then undergo enterohepatic recirculation, which again, is significantly regulated and affected by gut flora. Given the importance of gut flora in glycoside pharmacokinetics, concern has arisen that simultaneous administration of antibiotics with glycoside-containing herbs may alter efficacy or safety of these herbs. There is preliminary evidence that this may be a problem.

One common use for licorice is treatment of patients with peptic ulcer. Because *Helicobacter pylori* provokes many peptic ulcers, antibiotics are also often given to patients who have this infection. In a rat model, administration of a combination formula known as *Shaoyao-gancao-tang* that contains *Glycyrrhiza uralensis* (*gancao*, a close relative of *G. glabra* that also contains glycyrrhetic acid) with the anti-*H. pylori* antibiotics amoxicillin and metronidazole led to reduced plasma levels of glycyrrhizin compared with when the formula was given with cimetidine or scopolamine.<sup>3</sup> The researchers found that alterations in colon flora and subsequent interference with glycoside hydrolysis by these bacteria were directly related to the reduction in systemic glycyrrhizin levels in the rats.

It is known that antibiotics can alter the pharmacokinetics of digoxin, a cardiac glycoside, in humans. However, the effect is a tendency to increase the levels of digoxin in the body. Clarithromycin has been shown, for example, to alter gut flora in such a manner as to inhibit so-called presystemic metabolism of the glycoside.<sup>4</sup> It is estimated that 10% of the popula-



*Panax* spp. (ginseng).

tion has major inactivation of digoxin by gut flora.<sup>5</sup> The loss of this inactivation can lead to digoxin toxicity as levels of the glycoside build up in the body. Although inhibition of renal clearance of digoxin and decreased hepatic catabolism of digoxin by cytochrome P450 (CYP450) enzymes may also be involved, gut-flora effects are also often a factor.<sup>6</sup>

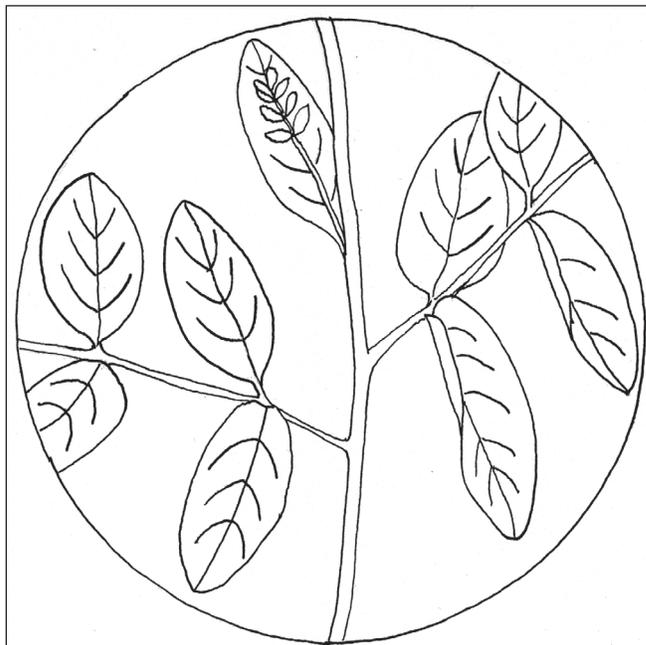
Preliminary studies with rats found that excretion of phenolic glycosides was altered in complex and often unpredictable ways by eliminating some or all gut flora organisms.<sup>7</sup> Specific organisms appeared to affect different glycosides differently, which is logical but dramatically increases the potential for unpredictable interactions given the sheer number of different organisms inhabiting the colon.

This complexity is confirmed in human studies involving the isoflavone glycosides, such as genistein and daidzein from *Glycine max* (soy). When children consumed antibiotics alone with soy nuts, overnight urinary excretion of genistein and total isoflavones decreased while there was a trend toward higher *O*-desmethylangolensin excretion.<sup>8</sup> This same protocol was repeated twice in adults and children at the same time, and different excretion patterns were seen in the two age groups.<sup>9,10</sup> Adults who consumed oral antibiotics with soy nuts had increased daidzein and total isoflavone urinary excretion, while children had reduced excretion of various isoflavones.

Many important botanical medicines contain glycosides or other constituents metabolized by gut flora, including but not limited to *Rheum palmatum* (Chinese rhubarb), *Gentiana lutea* (gentian), *Eleutherococcus senticosus* (eleuthero), *Panax ginseng* (Asian ginseng), *Arctostaphylos uva-ursi* (uva-ursi), and *Salix* spp. (willow). Research is needed with these and all other glycoside-rich herbs to find out how they interact with antibiotics.

## Tamoxifen

*Actaea racemosa* (black cohosh) root is a popular hormone-modulating herb used by many women for managing menopausal symptoms. There are many positive studies showing this herbal extract to be effective for relieving hot flashes, though



*Glycyrrhiza* spp. (licorice). Drawing © 2009 Kathy Abascal, B.S., J.D., R.H., (AHG).

these studies are not of the highest quality.<sup>11</sup> Tamoxifen is an estrogen-receptor antagonist used to prevent recurrence of hormone-sensitive cancers such as some breast cancers. Tamoxifen and other treatments for breast cancer commonly cause or exacerbate menopausal symptoms, particularly hot flashes, and so black cohosh is sometimes used simultaneously with the drug.

In a double-blinded trial, women with a recent history of breast cancer were randomized to receive either a standardized extract of black cohosh or placebo.<sup>12</sup> There was no effect of black cohosh extract on hot flashes in this study compared with placebo. A large percentage of the women in the study were taking tamoxifen. This has raised concerns that tamoxifen might block the effects of black cohosh. A similar and equally troubling result was seen in a large double-blinded trial involving the same extract of black cohosh, in which tamoxifen appeared to block the efficacy of the herb. The researchers drew this conclusion because the women who were taking tamoxifen did not have any benefits while some women who were not taking the drug did gain some benefits.<sup>13</sup>

At least one clinical trial did show that black cohosh was helpful for reducing hot flashes in breast-cancer survivors who were taking tamoxifen.<sup>14</sup> One major difference in this trial was that it ran for a full year instead of just 4–8 weeks like the two negative trials. Otherwise it used a similar extract at a similar dose as the other two trials.

Concern has been raised that black cohosh might stimulate estrogen-receptor positive (ER+) breast-cancer cell proliferation and thus be contraindicated in many patients who have breast cancer. However, many in vitro studies showing proliferation did not distinguish carefully between systems with and without estrogen present, or else these results were not noted and reported by people who read the studies. One good in vitro



*Glycine max* (soy).

study that shows that black cohosh is actually indicated was performed by Bodinet and Freudenstein.<sup>15</sup> When black cohosh extract was incubated with HR+ breast-cancer cells in vitro, the cells did not show increased proliferation, though other studies have reported that this can occur.<sup>16</sup> However, when estrogen was added to the system, proliferation of the cells was blocked.

What is more, in a very interesting twist, when tamoxifen was added along with estrogen and black cohosh, a synergistic inhibition of proliferation of the breast-cancer cells was seen. Given that most women have at least some circulating estrogen, though it is significantly decreased from premenopausal levels, black cohosh is unlikely to promote breast-cancer

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### *It is likely that acid-blocking drugs may interfere with herbs.*

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growth. None of the many clinical trials on black cohosh in breast-cancer survivors has ever reported an increased risk of recurrent breast cancer. Black cohosh's benefits for hot flashes may be blocked by tamoxifen, though it may work synergistically with the drug to prevent breast-cancer recurrence.

### **Acid-Blocking Drugs**

In a series of Japanese patients, those with the highest levels of stomach acid were found to respond the best to inflammation-modulating herbs of various types.<sup>17</sup> The hypothesis was that higher acid levels degraded polymeric herbal compounds better to smaller and better-absorbed units. This same group of researchers previously reported that heating herbs also improved their efficacy on these same grounds.<sup>18</sup> Given this and the probability that stomach acid is necessary for metabolism of some herbal constituents, then it is likely that acid-blocking drugs may interfere with herbs. As yet, no clinical trials have been found

assessing this concern, but they are sorely needed given the widespread use of these drugs.

In one trial, famotidine, a histamine-2 antagonist antacid drug was shown not to affect absorption of flavonoids from *Theobroma cacao* (chocolate) in humans.<sup>19</sup> It has been shown that stomach acid damages the activity of some herbs, such as the iridoid glycoside-rich inflammation modulator *Harpagophytum procumbens* (devil's claw).<sup>20</sup> In a situation such as this, an acid-blocking drug should not have a negative impact but rather have a positive impact. The adverse effects of these drugs do not warrant their use routinely with such herbs, but at least acid blockers do not appear to be contraindicated actively for use with such herbs.

### **Conclusion**

Present research is vastly incomplete but suggests that many pharmaceutical drugs can interfere with absorption or activity of a range of herbal medicines. If a patient is simultaneously taking herbs and drugs, and there does not seem to be a benefit from the herbs, then it would be logical to consider the possibility of interference by the pharmaceutical drugs as an explanation for the outcome. At such times, it might even be appropriate to discontinue use of a noncritical drug to allow a safer herb a chance to work. Ultimately, however, more research is needed to determine the extent and exact nature of drugs interfering with herbs in human beings. ■

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