St. John’s Wort: More Implications for Cancer Patients

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St. John’s wort (Hypericum perforatum L.) has been used as a medicinal plant in Europe and Asia for centuries. Although it is best known today for its use by patients with mild to moderately severe depression, St. John’s wort has also been used orally as a traditional treatment for excitability, neuralgia, fibrositis, sciatica, and anxiety and as a topical preparation for the treatment of wounds (1). Concerns over its use have been raised with the recognition that, whatever its beneficial health effects might be, St. John’s wort interacts powerfully with many important drugs, potentially mitigating their effects (1).

That herbal medicines may have adverse pharmacologic properties has come as a surprise to those who assumed that natural products must be safe. Yet, for products (be they synthetic drugs or complex herbal mixtures) to convey beneficial physiologic effects, we understand that the biochemical constituents in them must also harbor the risk for adverse effects. For herbal medicines, many such direct reactions are well described, including hypersensitivity reactions, liver toxicity, and coagulopathy (2). Herbal medicine–drug interactions were described only more recently.

In addition to St. John’s wort, a number of herbal remedies have been identified that affect synthetic drug metabolism and, potentially, drug efficacy. According to a recent systematic review (2), four of the seven top-selling herbal medicines in this country interfere with the metabolism or efficacy of approved synthetic drugs: Ginkgo biloba (ginkgo) may enhance or alter the effects of warfarin, thiazide diuretics, and trazodone. Panax ginseng (ginseng) interacts with alcohol, warfarin, and phenelzine. Allium sativum (garlic) changes the pharmacokinetics of paracetamol and warfarin and the effects of chlorpropamide. Piper methysticum (kava) alters or enhances the effects of levodopa and alprazolam.

Among these herbal medicines, the reports regarding drug interactions with St. John’s wort have been the most impressive. St. John’s wort induces highly promiscuous drug detoxification pathways and thus interferes with metabolism of many classes of drugs. Repeated administration of St. John’s wort results in potent and selective induction of cytochrome P450 (CYP) 3A in the intestinal wall and in the liver (3,4), apparently because the major constituent of St. John’s wort, hyperforin, is a ligand for the pregnane X receptor, which regulates expression of the CYP3A4 monoxygenase (5). Another constituent of St. John’s wort, hypericin, induces P-glycoprotein (Pgp)/MDR-1 expression in the intestinal wall in vitro and in vivo (3,6) and enhances the drug efflux function of Pgp (7). Hypericin also causes catalytic inhibition of human DNA topoisomerase II α in cell cultures (8).

The effects of St. John’s wort on drug levels have been confirmed in the clinic. A seminal study demonstrated that St. John’s wort statistically significantly lowers plasma concentrations of the human immunodeficiency virus-1 (HIV-1) protease inhibitor indinavir in normal volunteers, likely the result of CYP3A induction (9). After exposure to St. John’s wort, patients with HIV had increased plasma clearance of the non-nucleoside reverse transcriptase inhibitor nevirapine (10). These botanical–drug interactions are very disconcerting because the plasma level reductions of antiretroviral agents could expose affected patients to an increased risk for the development of viral drug resistance and disease progression. Similarly, in transplant patients, cyclosporin A levels were lower in patients taking St. John’s wort, likely the result of both Pgp activation and cytochrome P450 induction (11), which were associated with acute graft rejection in several patients (12). A recent case report

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associated taking St. John’s worth with diminished tacrolimus levels in a renal transplant patient. St. John’s worth also statistically significantly reduces plasma concentrations of the lipid-lowering agent simvastatin via CYP3A induction (14) and may increase the serotoninergic effects of triptans and selective serotonin reuptake inhibitors (SSRIs) (1).

Given the general effects of St. John’s worth on drug metabolism, its ingestion could be predicted to have profound implications for cancer therapy. Pgp induction is associated with drug resistance to anthracyclines, vinca alkaloids, epipodophyllotoxins and taxanes. Obviously, topoisomerase II α inhibition will result in decreased activity of etoposide, as well as of anthracyclines and dactinomycin. In fact, an undesirable interaction between St. John’s worth and cancer drugs has now been realized in the report by Mathijssen et al. (15) in this issue of the Journal. In an unblinded, randomized crossover study, five cancer patients were treated with irinotecan in the presence and absence of St. John’s worth. Plasma levels of the active metabolite of irinotecan, SN-38, statistically significantly decreased in patients taking St. John’s worth and taking St John’s wort. Mathijssen et al. conclude that patients taking irinotecan should avoid St. John’s worth, because irinotecan levels may be decreased by it, resulting in an increased risk of treatment failure.

Animals evolved formidable biochemical mechanisms to detoxify and eliminate otherwise harmful chemicals through their oxidation, conjugation, and excretion. These pathways afforded protection against potentially toxic foods long before drugs were invented. For many decades synthetic drugs largely displaced herbal medicines; thus, the issue of potential herb–drug interactions never loomed as a large one. With increased availability in the American marketplace and increased public consumption of herbal medicines over the past decade, however, the specter of herb–drug interactions has emerged as a credible public health problem. The report by Mathijssen et al. (15) extends our concerns to the field of cancer pharmacotherapeutics. Surveys have shown that cancer patients are among the most likely to seek complementary and alternative medical (CAM) remedies, including herbal medicines, with the hope that they would reduce the side effects of conventional treatments, extend life, or at least enhance quality of life (16). While awaiting outcomes of National Institutes of Health-funded studies of CAM practices in cancer patients, it would be prudent for patients and their oncologists to appreciate that, no matter how beneficial some approaches may appear to be, they are not all safe. Together, patients and oncologists should consider the options and develop a plan regarding which CAM practices to pursue and which to put aside altogether.

**References**


(2) Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. Drugs 2001;61:2163–75.


