2.2.These interactions could also lead to the reduced efficacy of manyClinical studies have suggested that Hypericum perforatum could lower the steady-state plasma concentration of many drugs, including amitriptyline, cyclosporine, tacrolimus, digoxin, fexofenadine, methadone, midazolam, styrene coumarin, saquinavir, simvastatin, theophylline, and warfarin, causing severe herbalprescription drug interactions.In addition, the administration of St. John's wort to healthy volunteers over 14 days resulted in an 18% reduction in digoxin exposure after a single dose of digoxin, and a 1.4- and 1.5-fold increase in the expression of duodenal P-gp and CYP3A4, respectively Although St. John's wort induces both P-gp and CYP3A4, like rifampin, the reduction in the oral bioavailability of digoxin may be caused by the induction of intestinal P-gp due to a lack of significant metabolism by CYP3A4 [33].Its crude extract is a complex mixture of multiple active substances, including hypericin, quercetin, isoquercetin, biflavonoids, hyperforin, procyanidin, catechin, tannin, and chlorogenic acid.St. John's wort extracts containing hyperforin increase the expression of CYP-enzymes and P-gp mainly in the gut and liver which leads to a clinically relevant decrease of the bioavailability of CYP and P-gp substrates.Also, minor changes in drug bioavailability observed in clinical studies for valerian, echinacea, ginkgo and hawthorne are clinically not relevant, although in vitro studies point to drug interactions in vivo.Most anticancer drugs undergo Phase I and/or II metabolism and are substrates of Pglycoprotein, breast cancer resistance protein, multidrug resistance (MDR) associated proteins, and/or other transporters.For example, a clinical study in cancer patients reported that treatment of St John's wort at 900 mg/day orally for 18 days decreased the plasma levels of the active metabolite of irinotecan, SN-38, by 42%.Coadministration of St. John's wort and the HIV protease inhibitor indinavir reduced the latter's exposure by 57% in healthy volunteers [35].Herb-drug Interactions in Drug Metabolism and Pharmacokinetics 2.2.1.

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