

Effect of St John's Wort on Drug Metabolism by Induction of Cytochrome P450 3A4 Enzyme

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ST JOHN'S WORT (*HYPERICUM PERFORATUM*) is an herbal product widely used to treat depression.¹ It is available without prescription in the United States and is taken mostly without medical recommendation or supervision. Some trials have supported St John's wort use in the treatment of mild to moderate depression.²⁻⁴ However, recent multicenter, double-blind, placebo-controlled studies did not support its effectiveness for moderate or severe depression.^{5,6}

A series of case reports and formal clinical studies indicate that St John's wort can participate in clinically significant and perhaps dangerous drug interactions. Documented St John's wort interactions include a diverse group of drugs including the immunosuppressants cyclosporine⁷ and tacrolimus,⁸ the protease inhibitor indinavir,⁹ the nonnucleoside reverse transcriptase inhibitor nevirapine,¹⁰ the tricyclic antidepressant amitriptyline,¹¹ the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor simvastatin,¹² the nonsedating antihistamine fexofenadine,¹³ and digoxin.¹⁴ St John's wort may also induce the metabolism of oral contraceptives containing ethinyl estradiol and result in unplanned pregnancy.^{15,16} These reports suggest an inductive metabolic effect on the cyto-

Context St John's wort is a popular herbal product used to treat depression but it has been implicated in drug interactions.

Objective To assess the potential of St John's wort administration to alter the activity of the cytochrome P450 (CYP) enzymes extensively involved in drug metabolism.

Design, Setting, and Participants Open-label crossover study with fixed treatment order conducted March 2002 to February 2003 in a US general clinical research center involving 12 healthy volunteers (6 men and 6 women) aged 22 to 38 years before and after 14 days of administration of St John's wort.

Intervention Participants were given probe drugs (30 mg of dextromethorphan and 2 mg of alprazolam) to establish baseline CYP 3A4 and CYP 2D6 activity. After a minimum 7-day washout period, participants began taking one 300-mg tablet 3 times per day. After 14 days of St John's wort administration, participants were given the probe drugs along with 1 St John's wort tablet to establish postadministration CYP activity; the St John's wort dosing regimen was continued for 48 hours.

Main Outcome Measures Changes in plasma pharmacokinetics of alprazolam as a probe for CYP 3A4 activity and the ratio of dextromethorphan to its metabolite, dextromethorphan, in urine as a probe for CYP 2D6 activity.

Results A 2-fold decrease in the area under the curve for alprazolam plasma concentration vs time ($P < .001$) and a 2-fold increase in alprazolam clearance ($P < .001$) were observed following St John's wort administration. Alprazolam elimination half-life was shortened from a mean (SD) of 12.4 (3.9) hours to 6.0 (2.4) hours ($P < .001$). The mean (SD) urinary ratio of dextromethorphan to its metabolite was 0.006 (0.010) at baseline and 0.014 (0.025) after St John's wort administration ($P = .26$).

Conclusions A 14-day course of St John's wort administration significantly induced the activity of CYP 3A4 as measured by changes in alprazolam pharmacokinetics. This suggests that long-term administration of St John's wort may result in diminished clinical effectiveness or increased dosage requirements for all CYP 3A4 substrates, which represent at least 50% of all marketed medications.

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chrome P450 (CYP) 3A4 enzyme and/or the drug efflux transporter P-glycoprotein.¹⁷ St John's wort induces CYP 3A4 and P-glycoprotein expression in vitro and in vivo.¹⁸⁻²⁰

The present study, conducted March 2002 to February 2003, assessed the effect of administration of a 14-day course of St John's wort on CYP 3A4 and CYP 2D6 activity in healthy volunteers. Cytochrome P450 3A4 and CYP 2D6 were chosen because together they are involved in the metabolism of approximately 70% of prescription and

over-the-counter medications.²¹ Dextromethorphan and alprazolam were chosen as CYP 3A4 and CYP 2D6 probe drugs, respectively, because they are pre-

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dominantly metabolized by these isoforms. Although overlap exists between CYP 3A4 and P-glycoprotein substrates, P-glycoprotein is not likely to play a significant role in the disposition of alprazolam.²² Both drugs are well tolerated and have been successfully used as probes for these enzymes in previous studies.²³⁻²⁹

METHODS

Participants

Twelve volunteers (6 men and 6 women) aged 22 to 38 years (mean [SD] age, 28.6 [5.5] years; mean [SD] weight, 72.9 [19.1] kg) provided written informed consent approved by the Medical University of South Carolina Office of Research Integrity. All volunteers were determined to be healthy by history, physical examination, and basic laboratory monitoring as described elsewhere.²⁸ All were nonsmokers, were taking no medications or supplements, and were asked to abstain from grapefruit juice, caffeine, and alcohol use during the study period. All participants were phenotyped with dextromethorphan and determined to be extensive metabolizers of CYP 2D6.³⁰

St John's Wort Product

The St John's wort product used in this study is the LI 160 formula marketed as Kira in the United States (Lichtwer Pharma, Eatontown, NJ). This formula has been used in 2 recent multicenter clinical trials assessing the effect of St John's wort in major depressive disorder.^{5,6} According to the label, each tablet contains 300 mg of a St John's wort extract standardized to 0.12% to 0.3% hypericin. This study used a single lot that was analyzed for major constituents; we used the recommended dosage of 1 tablet 3 times per day (8 AM, noon, and 8 PM).

Study Design

This was an open-label crossover study with a fixed treatment order. The study consisted of a baseline CYP activity assessment, a 14-day St John's wort administration period, and a postadministration CYP activity assessment. The

fixed-order design was chosen to minimize washout time and intra-individual variability between study phases. This design ensured that potential carryover effects on CYP activity from prior St John's wort administration were not observed during the baseline phase. The study was approved by the university's institutional review board.

Baseline CYP Activity Assessment

Participants were admitted to the Medical University of South Carolina General Clinical Research Center (GCRC). Following an overnight fast and urinary void, each participant was given 30 mg of dextromethorphan (Robitussin, Wyeth Consumer Healthcare, Madison, NJ) along with 2 mg of generic alprazolam (Mylan, Morgantown, WVa) orally with water. Participants were fed a standard breakfast 30 to 45 minutes following drug administration. An 8-hour urine collection commenced immediately after probe drug administration. Blood samples (10 mL) were collected in heparinized tubes immediately prior to the administration of alprazolam and again 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 60 hours afterward. Following medical clearance, participants were discharged from the GCRC and returned for the final blood draws. Plasma was stored at -70°C until analysis.

St John's Wort Dosing Phase

Following a minimum 7-day washout period, participants were provided a supply of St John's wort tablets in blister packaging with instructions to take one 300-mg tablet 3 times per day for 14 days.

Posttreatment CYP Activity Assessment

After 14 days of administration of St John's wort, participants were readmitted to the GCRC. Probe drug administration, specimen collection, and meals were identical to those of the baseline assessment except that 1 St John's wort tablet was administered concomitantly with the probe drugs and the normal St John's wort dosing

regimen was continued until the 48-hour time point. One week later participants returned for a follow-up exit visit and basic laboratory monitoring.

Laboratory and Statistical Analyses

High-performance liquid chromatographic analysis of St John's wort tablets for hypericin, pseudohypericin, and hyperforin was performed on 5 tablets from the lot used in this study. Hypericin and pseudohypericin were separated isocratically (volume ratio: 22% methanol, 38% tetrahydrofuran, 40% aqueous H_3PO_4 [0.1% solution at pH 4.0]; flow rate: 0.75 mL/min) using a Luna C8 250 \times 4.6 mm, 5- μm high-performance liquid chromatograph column (Phenomenex, Torrance, Calif) with fluorescence detection (315 nm; 590 nm). Hyperforin was separated isocratically (volume ratio: 5% water, 15% methanol, 80% acetonitrile; flow rate: 1.0 mL/min) using a Phenomenex Luna C18 250 \times 4.6 mm, 5- μm column with detection at 315 nm. Hyperforin and hypericin were identified by comparison of retention time with the analytic standards (Sigma, St Louis, Mo). Pseudohypericin was tentatively identified and quantitated in hypericin equivalents. Dextromethorphan, its CYP 2D6-dependent metabolite dextrorphan, and alprazolam were determined using previously described high-performance liquid chromatographic methods.^{31,32}

Noncompartmental, nonlinear, least square regression analysis of alprazolam plasma concentrations was performed using WinNonLin (Pharsight Corp, Cary, NC).²⁸ An assumption test indicated that the data were normally distributed and appropriate for this analysis. Pharmacokinetic parameters for alprazolam and dextromethorphan to dextrorphan metabolic ratios (DMRs) were evaluated for statistically significant differences between baseline and postadministration values by the paired, 2-tailed *t* test. This study had 80% power to detect a 20% difference in the area under the curve (AUC) of alprazolam and a 120% difference in the DMR values with $P \leq .05$.

Table. Pharmacokinetic Parameters for Alprazolam at Baseline and After Administration of St John's Wort*

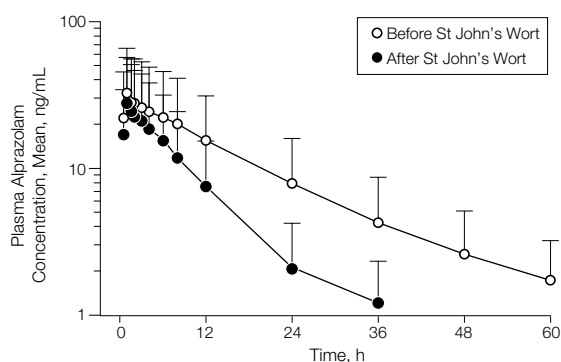
Parameters	All			Men			Women		
	Baseline	After St John's Wort	P Value	Baseline	After St John's Wort	P Value	Baseline	After St John's Wort	P Value
AUC _{0-inf} , ng/mL × h†	565 (121) [488-642]	262 (71) [216-307]	<.001	583 (137) [439-726]	264 (89) [171-358]	<.001	547 (112) [430-665]	259 (56) [200-317]	<.001
AUC, ng/mL × h‡	522 (103) [416-629]	254 (67) [198-311]	<.001	522 (114) [401-642]	254 (84) [165-342]	<.001	523 (101) [416-629]	254 (53) [198-311]	<.001
Oral clearance, L/h	3.7 (0.9) [3.2-4.3]	8.4 (3.2) [6.3-10.5]	<.001	3.6 (0.9) [2.7-4.5]	8.7 (4.4) [4.1-13.4]	.02	3.8 (0.9) [2.8-4.8]	8.1 (1.9) [6.1-10.1]	.001
Half-life, h	12.4 (3.9) [9.9-15.0]	6.0 (2.4) [4.5-7.6]	<.001	14.6 (4.2) [10.0-18.9]	6.8 (3.2) [3.4-10.2]	.008	10.4 (2.6) [7.7-13.1]	5.2 (1.0) [4.2-6.1]	.002
C _{max} , ng/mL	34 (9) [28-39]	31 (7) [27-35]	.39	33 (13) [20-47]	27 (5) [21-35]	.21	34 (5) [29-39]	36 (4) [31-40]	.34
T _{max} , h	1.1 (0.5) [0.8-1.5]	1.3 (0.6) [0.9-1.6]	.62	0.8 (0.4) [0.4-1.3]	1.4 (0.8) [0.6-2.3]	.16	1.4 (0.5) [0.9-1.9]	1.1 (0.4) [0.7-1.5]	.24

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration of alprazolam in plasma; T_{max}, time to reach maximum concentration of alprazolam in plasma.

*Data are expressed as mean (SD) [95% confidence interval].

†The AUC_{0-inf} is for alprazolam plasma concentration vs time from time 0 to infinity.

‡The AUC is for alprazolam plasma concentration vs time from time 0 to the last measurable time point as determined by the trapezoidal rule.

Figure. Area Under the Curve for Plasma Alprazolam Concentration vs Time at Baseline and After St John's Wort Administration (n = 12)

Profiles are shown representing mean (SD) alprazolam concentrations in plasma following administration of alprazolam, 2 mg, before and after administration of St John's wort, one 300-mg tablet 3 times per day for 14 days. No participant had detectable concentrations of alprazolam at the 48-hour time point after administration of St John's wort.

RESULTS

All 12 participants completed the study. As expected, all participants experienced sedation following alprazolam administration. No participant reported an unanticipated or serious adverse event associated with St John's wort administration or other aspects of the study.

The St John's wort product used in this study contained a mean (SD) of 1398 µg (105 µg) of hyperforin as well as 151 µg (19 µg) of hypericin and 279 µg (24 µg) of pseudohypericin in each tablet.

All participants metabolized dextromethorphan extensively to its metabolite, dextrorphan, at baseline and after 14 days of St John's wort administra-

tion. The DMR value was increased from the baseline value for 6 participants and was decreased for the other 6 participants. The mean (SD) urinary ratio of dextromethorphan to its metabolite was 0.006 (0.010) at baseline and 0.014 (0.025) after St John's wort administration ($P = .26$).

Pharmacokinetic measurements obtained at baseline and following St John's wort administration are summarized in the TABLE. A 2-fold decrease in the AUC for alprazolam plasma concentration vs time ($P < .001$) and a 2-fold increase in alprazolam clearance ($P < .001$) were observed following St John's wort administration. The mean (SD) alprazolam elimination half-life was shortened from 12.4 (3.9) to

6.0 (2.4) hours ($P < .001$). The AUCs for plasma alprazolam concentration vs time at baseline and after St John's wort administration are shown in the FIGURE. After 36 hours, only 7 of 12 participants had measurable alprazolam concentrations after St John's wort administration vs all 12 participants at baseline. At 48 hours, no participant had measurable alprazolam concentrations after St John's wort administration compared with 11 of 12 participants during the baseline phase. Significant decreases in the alprazolam elimination half-life and AUC and increases in clearance were observed when data were separated by sex and analyzed separately for men and women. No significant differences between baseline and post-St John's wort periods were noted in the maximum concentration of alprazolam in plasma or the time to reach it.

COMMENT

In this study, we observed a 2-fold increase in alprazolam clearance after administration of St John's wort for 14 days. The increase in alprazolam clearance appears to be due to CYP 3A4 induction. Cytochrome P450 3A4 is involved in the metabolism of approximately 50% of all currently used medications.^{17,33,34} These findings indicate that long-term administration of St John's wort may result in diminished clinical efficacy or increased dosage requirements for a large and diverse group of medications metabolized by CYP 3A4.

The degree of CYP 3A4 induction produced by St John's wort exposure can be compared with previous studies using the potent CYP 3A4 inducers rifampin and carbamazepine. Carbamazepine decreased the elimination half-life of alprazolam from 17.1 hours to 7.7 hours,³⁵ whereas rifampin reduced it from 14.1 hours to 2.6 hours.²⁶ In the present study, St John's wort reduced the elimination half-life of alprazolam from 12.4 hours to 6.0 hours ($P < .001$). The reductions in alprazolam elimination half-life by St John's wort could be entirely due to CYP 3A4 induction in the liver, although CYP 3A4 is expressed in many tissues, including the small intestine. The oral bioavailability of alprazolam is between 80% and 100%, so significant enteric metabolism at baseline is unlikely.³⁶ The present study design did not make possible the determination of whether the changes in alprazolam disposition were due to increased hepatic or enteric metabolism or both.

Earlier in vitro studies indicated inhibition of CYP 3A4 by St John's wort.^{13,37} Our previous study, designed to measure only inhibition of CYP 3A4, demonstrated that a 3-day dosing period with St John's wort produced no significant effect on CYP 3A4 activity, although a trend toward CYP 3A4 induction was observed.³⁸ While single doses and short-term dosing of St John's wort appear to have little effect on CYP 3A4 activity, this study and others indicate significant CYP 3A4 induction after dosing with St John's wort for periods of 10 or more days.^{7-12,38,39} The time course of CYP 3A4 induction by St John's wort as well as any dose-response effects should be considered in future studies.

Repeated dosing of St John's wort did not significantly alter CYP 2D6 activity, as indicated by the DMR. Although a mean 2-fold increase in the DMR was observed following St John's wort administration ($P = .26$), half of the participants showed an increase in the DMR while the other half showed a decrease. The magnitude of the observed changes reflects normal variability in dextro-

methorphan metabolism.⁴⁰ Quinidine is a potent CYP 2D6 inhibitor that increases the DMR by more than 100-fold.⁴⁰ Less potent but clinically relevant CYP 2D6 inhibitors such as paroxetine, sertraline, and fluoxetine increase the DMR by 8- to 55-fold.⁴¹ Although this study was not designed to detect very modest changes in CYP 2D6 activity, we conclude that long-term St John's wort administration does not have effects on CYP 2D6 activity that are likely to be of clinical significance.

St John's wort, like most herbal products, contains a large array of biologically active compounds.⁴² Major constituents include the phloroglucinol derivative hyperforin, which induces CYP 3A4 in vitro,¹⁸ and the naphthodianthrones pseudohypericin and hypericin.^{43,44} It was beyond the scope of this study to measure the presence of major St John's wort constituents in plasma, but limited pharmacokinetic data are available from other studies.^{45,46} The major constituents of the St John's wort product used in this study were documented. This is essential when performing clinical studies with herbal products because substantial variability and deviation from labeled claims have been reported for herbal products, including St John's wort.^{44,47}

In conclusion, repeated dosing with St John's wort does not appear to have significant effects on CYP 2D6 activity but results in substantial induction of CYP 3A4 activity. These results indicate that long-term administration of St John's wort may result in diminished clinical effectiveness or increased dosage requirements for all CYP 3A4 substrates, which represent at least half of marketed medications. These findings underscore the potential problems associated with the widespread practice of using herbal products concomitantly with conventional medications.

Author Contributions: As principal investigator of the study, Dr Markowitz had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analyses. *Study concept and design:* Markowitz, Donovan, DeVane. *Acquisition of data:* Markowitz, Donovan, Taylor, Ruan.

Analysis and interpretation of data: Markowitz, Donovan, DeVane, Taylor, Wang, Chavin.

Drafting of the manuscript: Markowitz, Donovan.

Critical revision of the manuscript for important intellectual content: Markowitz, Donovan, DeVane, Taylor, Ruan, Wang, Chavin.

Statistical expertise: Donovan, DeVane.

Obtained funding: Markowitz.

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Study supervision: Markowitz, Donovan, DeVane, Chavin.

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The greatest thing in the world for a man to know is how to be himself.

—Michel Eyquem de Montaigne (1533-1592)