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P-glycoprotein expression is increased by St. John's Wort: Consequences for medication interactions

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Although Rims St. John's Wort (SJW) is frequently used to treat depression, there are worries that it may interfere with other medications. Indinavir and cyclosporin trough plasma concentrations have significantly decreased when co-administered with SJW [1, 2]. The most likely mechanism of interaction has been identified as induction of cytochrome P450 3A4 (CYP3A4). The size of the interaction observed in clinical practice, however, is more than what in vitro research indicated, indicating the possibility of further interaction pathways. Since cyclosporin and indinavir are substrates for both CYP3A4 and the multidrug transporter P-glycoprotein, we postulated that SJW's modification of P-glycoprotein expression and activity could lead to the emergence of potentially dangerous drug-drug interactions.

MetSods Healthy volunteers were randomized to either a placebo (n = 7) or SJW (0.15%) 600 mg three times a day for 16 days (n = 15). At baseline, 16, and 32 days after therapy, blood samples were taken to measure P-glycoprotein expression and function. Using Ficoll density gradient centrifugation, peripheral blood lymphocytes (PBMCs) were separated, dried, and permeabilized. A P-glycoprotein specific antibody was used to stain the cells, and the median fluorescence intensity (MFI) values were measured using flow cytometry. As controls, vimentin and IE (nonsense antibody) were employed. RT-PCR confirmed the existence of the MDR 1 gene product. Rhodamine efflux was used to calculate P-glycoprotein-mediated drug efflux both with and without ritonavir. The data underwent nonparametric analysis and are presented as mean±s.d.

Results In participants treated with SJW, P-glycoprotein expression rose 4.2 times from baseline (7.0±1.9 vs. 29.5±14.3 (MFI); $P<0.05$). Placebo had no impact (5.1±1.3 vs. 6.0±1.9 MFI). In comparison to baseline, SJW enhanced P-glycoprotein-mediated rhodamine efflux (lower ratio) (0.12±0.04 vs. 0.24±0.18 $P<0.05$). With a placebo, nothing changed. Rhodamine accumulated more intracellularly in both groups when Ritonavir (5 μM) blocked P-glycoprotein-mediated efflux. However, after receiving SJW, this effect was lessened (23.9±15.3% vs. 75.4±16.4% $P<0.05$).

In PBMCs of healthy volunteers, Gonclusions SJW boosted the expression of the multidrug transporter P-glycoprotein and improved its drug efflux capability. This could explain the differences between in vitro and in vivo data and provide as a second explanation for the drug-herb interactions observed in clinical practice. Patients taking medications that are P-glycoprotein substrates should be cautioned against self-medication with SJW due to the possibility of clinically significant drug interactions because P-glycoprotein and CYP3A4 have different but overlapping substrates.

Keywords*:* P-glycoprotein, ritonavir, flow cytometry, and St. John's Wort

Introdπction

For generations, people have utilized St. John's Wort (Hypericum perforatum) as a herbal cure [3]. Galen (A.D. 150–200) is credited with prescribing it for menstrual problems. It was also used to treat depression in the Middle Ages, earning its well-known moniker since it blooms on June 24, St. John the Baptist's birthday. Recently, St. John's Wort (SJW) has become known as "nature's Prozac," and at least two randomized controlled clinical trials have shown that it is just as effective as traditional antidepressant treatment [4-6].

With over 2.7 million prescriptions written annually, it is presently the most widely prescribed antidepressant in Germany [7]. Although SJW is widely used, little is known about its pharmacokinetic characteristics, and because it is typically supplied as an over-the-counter herbal treatment, it has not undergone the thorough clinical research necessary for other substances [8].

Furthermore, until recently, the interaction potential of SJW was widely disregarded due to the public's belief that everything "natural" is harmless [9]. The possibility of SJW interacting with coadministered medications should be taken seriously because 18.4% of U.S. adults surveyed reported using at least one herbal product or high dose vitamin concurrently with regular prescription medications, but over 60% did not tell their doctors about such use [10]. By accelerating the metabolism of coadministered medications including warfarin and the oral contraceptive pill, SJW may result in clinically significant interactions, according to a number of recent investigations [8]. Acute transplanted organ rejection developed as a result of chronic coadministration of SJW, which decreased plasma cyclosporin concentrations by approximately 80% [2]. In a similar vein, injection of the HIV 1 protease inhibitor indinavir resulted in an 81% decrease in indinavir via plasma concentrations [1]. Digoxin coadministration, on the other hand, resulted in a 30% decrease in plasma digoxin concentrations [11, 12]. The most plausible explanation for these interactions is that SJW induces hepatic CYP 3A4, and in vitro research shows that SJW roughly doubles CYP3A4 expression [13, 14, 15]. Furthermore, the hypothesized active component of SJW, hyperforin, is a strong ligand for the pregnane X receptor, an orphan nuclear receptor that controls CYP3A4 production [16, 17]. It's interesting to note that the magnitude of the interaction observed in clinical reports (80%) is larger than that predicted by in vitro data (50%), indicating the possibility of a second interaction mechanism. Additionally, since digoxin primarily undergoes renal clearance with metabolism by CYP3A4 providing a minor metabolic pathway, induction of CYP3A4 is unlikely to fully explain this interaction. Digoxin, indinavir, and cyclosporin are known to be substrates for the multidrug transporter P-glycoprotein, which acts as a transmembrane drug efflux pump, in addition to being substrates for CYP3A4 [18–21]. We hypothesize that SJW may change P-glycoprotein expression and/or activity, lowering tissue or cellular concentrations of specific medications and increasing the possibility of drug-drug interactions. Peripheral blood cells (PBMCs) from healthy people were selected as the paradigm for this study because lymphocytes express functioning P-glycoprotein but not functional CYP3A4.

Methods

Study design

A single blind, randomized, placebo-controlled trial involved twenty-two healthy volunteers, thirteen of whom were female. After giving their informed consent, 15 volunteers were given SJW (Good n' Natural 0.15% standardized extract 600 mg three times daily) for 16 days, while seven subjects were given a placebo. Throughout the trial, smoking and concurrent drug usage (including the oral contraceptive pill) were forbidden.

Every participant was observed for the emergence of side symptoms that are frequently linked to SJW, such as constipation, gastrointestinal distress, and dry mouth.For P-glycoprotein expression and function, venous blood samples were taken at baseline, 16 days, and 32 days (16 days after stopping medication). Additionally, a conventional h.p.l.c. method detailed subsequently was employed to assess the hypericin content of each batch of SJW used in the study.

lymphocyte isolation

Ficoll density gradient centrifugation was used to separate peripheral blood mononuclear cells (PBMCs) from venous blood in less than two hours. In summary, whole blood was placed onto Lymphoprep (Gibco USA) and centrifuged for 25 minutes at 1200 rev min—1, 4° C. Hanks balanced salt solution without calcium and magnesium (Life Technology, Paisley, U.K.) was used to remove the buffy coat, resuspend it, and wash it twice (2000 rev min—1×5 min).

Finally, 10% fetal calf serum (FCS; Sigma, Poole, Dorset) was added to the culture medium (RPMI plus glutamine; Life Technology, Paisley, U.K.) in which the cells were resuspended. Following staining with ethidium bromide/acridine orange, cell viability and count were measured in a Neubauer's chamber. Aliquoted cells (1×106 cell ml—1) were set aside for RNA isolation and P–glycoprotein expression and function.

The presence of P-glycoprotein was identified by flow cytometry and confirmed by RT-PCR in compliance with the St Jude consensus recommendations [22] concerning the methodology and interpretation of P-glycoprotein expression and function. Cells were permeabilized with 0.05% (w/v) saponin (Sigma) after being dyed in 2% paraformaldehyde (Celldx, Becton Dickinson, Mountain View, CA) for 20 minutes at room temperature. A JSB1 monoclonal antibody (Sanbio, Uden, Netherlands) that targets a highly conserved intracellular P-glycoprotein epitope was used to label cells for 30 minutes at 37° C. While an antibody to the cytoskeletal component vimentin (Dako AS, Glostrup, Denmark) was used as a control for the permeabilization technique, a negative fluorescence control was carried out using mouse monoclonal IE immunoglobulin (Ig)G derived from a murine hybridoma supernatant (ATCC, Manasses V.A.) HB179, 30 min, at 37° C.

Cells were incubated with 100 µl rabbit antimouse fluorescein labelled isothiocyanate (FITC)–conjugated F(ab)2 (1: 50 dilution; Dako AS, Glostrup) for 30 minutes at 37° C after excess antibody was removed by washing with 0.05% (w/v) saponin. After removing any remaining antibody, the cells were resuspended in 0.5 ml of paraformaldehyde and flow cytometric analysis was performed to determine the median fluorescence intensity values (MFI), a measure of expression. RT PCR was used to confirm the presence of MDR1 mRNA in each sample, as previously reported [23].

Functional studies of rhodamine t23 transport: efflux and inhibition

Methods: Rhodamine 123 (1.25 µg ml—1; Sigma) was added to PBMCs (1×106) cells for 25 minutes at 37° C in RPMI 1640 supplemented with 10% FCS. To enable dye efflux, cells were incubated for three hours at 37° C in three milliliters of dye-free medium after being twice washed in ice-cold solution. An aliquot was taken at baseline, t=0 (maximum loading), and three hours later, t=180 min (maximum efflux). It was then washed twice in ice-cold medium (3 min×2000 rev min—1) and dried in ice-cold paraformaldehyde (Celldx). Flow cytometric analysis was used to measure cellular fluorescence, which was then expressed as median fluorescence intensity.

Flow cytometry: The lymphocytes displayed in side scatter and forward scatter were electronically gated and obtained (10,000 events) via either the FL2 channel (function) or the FL1 channel (expression). A histogram of FL1 or FL2 staining inside the gate was used to plot the quantity of fluorescence. Cellquest software (WINMDI version 2.6) was used for data acquisition in order to calculate median fluorescence intensity values.A known P-glycoprotein inhibitor, ritonavir (5 µM), was used in parallel trials. This concentration was selected based on a previously established dose response curve for ritonavir's suppression of P-glycoprotein-mediated rhodamine efflux in healthy volunteers' PBMCs (unpublished data). Abbott Laboratories donated ritonavir.

Reverse transcription-polymerase chain reaction (RT-PCR)

Using Tri Reagent (Sigma), the Chomczynski & Sacchi [24] method was modified to isolate whole cellular RNA from PBMCs. Using random decamers and M-MLV reverse transcriptase (Reverse-iT kit, Abgene), first strand cDNA was created from 2 µg of total RNA. Using a typical PCR procedure and gene specific primers (Table 1), as reported by Egashira et al. [23], the resulting cDNA was amplified by PCR. Every PCR reaction was carried out twice. Ethidium bromide was used to stain the PCR results after they were electrophoresed on a 2.0% (w/v) agarose gel. Gels were photographed, examined under UV light, and examined using Gene Tools analysis software (Syngene) on a computer.

Hypericin assay

Chi & Franklin's method served as the foundation for the h.p.l.c. approach [25, 26]. In summary, a C–8 column (15×4.6 mm, 5 µm; column temperature: 60° C) with a Shimadzu LC–10AS pump (flow rate: 1.5 ml min—1) and a Shimadzu RF–10AXL fluorescence detector (Ex 390 nm; Em 620 nm) was used to test hypericin (Fluka Chemie AG, Buchs, Germany). A stock solution of hypericin (1 mg ml—1) produced in DMSO was serially diluted with the h.p.l.c. mobile phase (0.03 M phosphate buffer (pH 7) and methanol (30:70, v/v)) to create a standard curve. After dissolving a 10 mg aliquot of each St. John's Wort pill (0.15% extract) in one milliliter of DMSO, the mixture was centrifuged for five minutes at 2000 revolutions per minute. Before injection, the supernatant was taken out and diluted (1: 100) with mobile phase.

For 10 µg ml—1 and 50 µg ml—1, the intra-day coefficients of variation (n=4) were 3.1% and 2.2%, respectively. At these concentrations, the inter-day coefficients of variation (n=8) were 3.5% and 4.3%, respectively.

Data analysis

P–glycoprotein expression was calculated as the difference between the median fluorescence intensities following labelling with JSB1 and IE for each sample.

Table 1 Sequences of upstream and downstream oligonucleotide primers.

mRNA	*Forward*	*Reverse*	*Tm*	*Number of cycles*
β_2M	ACCCCCACTGAAAAAGATGA	ATCTTCAAACCTCCATGATG	55° C	32
MDR–1	CCCATCATTGCAATAGCAGG	GTTCAAACTTCTGCTCCTGA	55° C	34

P–glycoprotein function was expressed as the ratio $t180/t\ 0$ (maximum efflux/maximum loading), therefore a reduced ratio indicates enhanced drug efflux function. The percentage of reversible efflux in the presence of ritonavir (an inhibitor) was calculated as:

$$100x\ \frac{Rit180 — t180}{t0 — t180}$$

Statistical analysis

Data were subjected to nonparametric analysis for paired (Wilcoxon), unpaired (Mann Whitney U) *t*–tests or a one– way analysis of variance followed by multiple comparison (Dunn's test) where appropriate. Data are expressed as mean±s.d. $P<0.05$ indicates statistical signidcance.

Resπlts

Two capsules from each of the three SJW batches were subjected to duplicate analysis. They were discovered to have 0.15, 0.14, and 0.15% (w/w) hypericin, which is consistent with the producers' stated amount. Twelve of the fifteen subjects who were initially randomly assigned to receive SJW finished the study. Two participants were withdrawn due to the requirement for a possibly interfering medication, and one person stopped taking SJW because of side effects (dry mouth, nausea). The trial was completed by all seven healthy volunteers who were randomly assigned to receive a placebo.

We have previously demonstrated that P-glycoprotein expression in vivo is normally distributed (KS value=0.07; n=77; mean±s.d.; 7.82±3.2, unpublished data) and stable over two months in resting peripheral blood lymphocytes of healthy individuals under identical experimental conditions (i.e., nonsmoking and non-medicated). In the current investigation, participants treated with SJW for 16 days showed a mean 4.2-fold increase in P-glycoprotein expression compared to baseline values (29.5±14.3 vs 7.0±1.9 MFI; P<0.05; Figure 1a; 95% CI: 13.5, 31.6). On the other hand, P-glycoprotein expression in PBMCs treated with a placebo did not change (5.1±1.3 vs. 6.0±1.9 MFI; Figure 1a, c; 95% CI: –0.6, 2.4). Regarding elevated P-glycoprotein expression after SJW, there was significant individual variation (Figure 1b; range: 1.09–9.06 MFI). 16 days after stopping SJW, P-glycoprotein expression had returned to baseline (8.5±4.8 MFI; Figure 1a). In comparison to baseline levels, treatment with SJW increased P-glycoprotein mediated rhodamine efflux (lower ratio) (0.12±0.04 versus 0.24±0.18; P<0.05; 95% CI: 0.01, 0.29; Figure 2a). Placebo did not alter P-glycoprotein function (0.16±0.17 vs. 0.24±0.11; 95% CI: —0.05, 0.21; Figure 2b). Ritonavir (5 μM) significantly reduced P-glycoprotein mediated rhodamine efflux in the PBMCs of patients before to SJW administration compared to post-treatment values (75.4±16.4 vs. 23.9±15.3%; P<0.01; 95% CI: 43.7, 70.1; Figure 3). Prior to and following placebo therapy, the percentage inhibition by ritonavir was comparable.

Non-quantitative RT-PCR was used to confirm the presence of MDR1 mRNA. In every sample obtained, amplidcation products of the anticipated size [23] were found in PBMCs at 167 base pairs for MDR1 and 120 base pairs for b2 microglobulin.

Discπssion

P–glycoprotein is an energy dependant membrane– associated multidrug efflux pump encoded by the MDR–1 gene on the long arm of chromosome 7. Increasing multidrug resistance is associated with altered expression of P–glycoprotein, which then actively trans– ports drug substrates out of the cell lowering their intracellular drug concentration and facilitating the devel– opment of drug resistance [21, 27–29]. P–glycoprotein is differentially expressed in a variety of normal tissues including gut epithelium and peripheral blood lympho– cytes [30]. Many drugs including methotrexate, protease inhibitors, and steroids in addition to some cytotoxic agents are known to be substrates for this drug efflux mechanism. Therefore, their disposition and metabolism will be affected by its expression and activity [18, 28, 31–33]. A number of noncytotoxic compounds are capable of reversing the drug efflux effect including verapamil, cyclosporin and more recently the anti HIV drug ritonavir [29, 34, 35]. Inhibition of the efflux pump may facilitate accumulation of drugs within previously resistant cells, improving drug bioavailability, intracellular concentrations and penetration into sanctuary sites such as the central nervous system [32, 36].

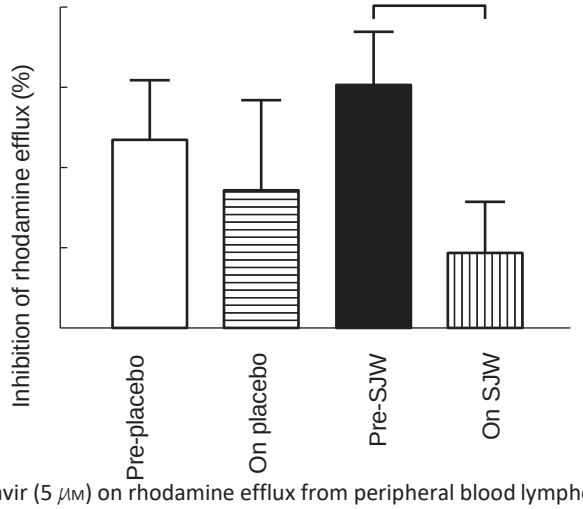
Recent reports have documented clinically relevant drug interactions between SJW and coadministered drugs such as indinavir, cyclosporin and digoxin [1, 2, 12], attributing induction of hepatic CYP3A4 as the likely mechanism [14, 15]. However, interactions with digoxin are unlikely to be fully explained by this mechanism, as it is not a CYP3A4 substrate. Furthermore, the discrepancy between *in vitro* and clinical data suggests that a second interaction mechanism may be involved. It has been postulated that drug interactions with SJW may be mediated through P–glycoprotein [1, 37]. The present study assesses the effects of chronic administration of SJW on P–glycoprotein expression and function in human PBMCs. We found that chronic treatment with SJW produced a greater than 4 fold increase in expression of the multidrug transporter P–glycoprotein in the PBMCs of healthy volunteers.

This was associated with enhanced drug efflux function resulting in reduced intracellular accumulation of rhodamine. Furthermore, in the presence of increased P–glycoprotein expression the inhibitory effects of ritonavir (a potent P–glycoprotein inhibitor)[38] were attenuated. Our data supports those of Durr *et al.* which showed a 1.4 fold increase in intestinal P–glycoprotein/MDR1 expression following chronic oral administration of SJW [37].

Furthermore, Greiner *et al.* [39] demonsrated a reduction in plasma digoxin concentrations following a similar inductive response to oral treatment with rifampicin suggesting P–glycoprotein induction as an alternative mechanism for drug–drug interactions. Our study provides further evidence of a second mechanism by which SJW may interact with coadministered drugs. Since P–glycoprotein and CYP3A4 and have distinct though overlapping substrates the magnitude of interactions encountered clinically may depend on whether a drug is transported mainly by P–glycoprotein (digoxin, colchicine), or metabolized by CYP3A4 (cimetidine, oral contraceptive pill), or both (indinavir, ritonavir, cyclosporin). Our data and that of others [14, 40] would suggest that CYP3A4 and P–glycoprotein expression may be coinduced by SJW. Studies indicate that St John's Wort induces hepatic drug metabolism through activa– tion of the pregnane X receptor [16], and have identidedPXR response elements in the upstream regulatory regions of these genes [17, 41–44]. In addition Geick *et al.* have recently identided a distinct DR4 nuclear receptor response element that is essential for MDR1 induction by rifampicin [45]. Whether the inductive response to St John's Wort seen in PBMCs is via an interaction with the PXR receptor was not addressed in the present study.

In recent years the therapeutic potential of P–glycoprotein modulation has been re–examined and at least one specidc inhibitor (valspodar) is presently undergoing clinical trials for use in oncology [11, 46]. Similarly low dose ritonavir has been added to some HIV antiretroviral salvage therapies in an effort to enhance efdcacy [28, 31, 47, 48]. Our dnding that chronic administration of SJW reduces the potential of ritonavir to inhibit P–glycoprotein mediated drug efflux suggests that the clinical use of P–glycoprotein modulators such as ritonavir or valspodar (PSC833) may be limited in the presence of SJW. In conclusion, when prescribing drugs, that are substrates of P–glycoprotein, CYP3A4 or both, patients should be informed about the risk of the chronic coadministration of SJW, which may give rise to clinically signidcant drug–drug interactions.

figπre 2 P–glycoprotein function expressed as the ratio of rhodamine efflux at time 0 and 180 min (*t*180/*t* 0) in peripheral blood lymphocytes of subjects pre– and post– 16 days treatment with either (a) St John's Wort or (b) placebo. Data are expressed as mean±s.d. **P*<0.05 compared with pre– St John's Wort.



Figπre 3 Effect of ritonavir (5 μM) on rhodamine efflux from peripheral blood lymphocytes of subjects pre– and post– 16 days treatment with either St John's Wort or placebo. Data are expressed as mean±s.d. **P*<0.05 compared with pre– St John's Wort.

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