

Hypericum Interactions - An Update

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Interactions of a high-dose (hyperforin-rich) extract of St. John's wort (*Hypericum perforatum*) with various drugs (theophylline, cyclosporine, warfarine, ethinylestradiol/desogestrel, amitryptiline) have been reported in recent years. Each of these drugs is metabolised by hepatic CYP microsomal oxidase enzymes. In relation to the wide-spread use of St. John's wort as a mild antidepressant, the spontaneous reports of interactions are very rare: 16 spontaneous ADRs have been reported with shortened bleeding time in patients under therapy with phenprocoumon and Yarsin®, which is estimated as 2 reports per million treatments with Yarsin®. Spontaneous reports indicating interactions with ovulation inhibitors and with cyclosporine A are estimated as 1 per million treatments (Schulz 2000).

Despite the fact that the use of St. John's wort has been at a high level for more than a decade, the known ADRs have been reported within recent years. The dosage of St. John's wort with respect to the plant extract itself, as well as the concentrations of hypericin and in the last few years also hyperforin, have been increasing; concentrations of hyperforin in plants and formulations are today higher due to late harvest.

But there are also two reports on transplant rejection (Ruschitzka et al. 2000), giving consideration to consequences of safety restrictions; the situation is also still confused because St. John's wort preparations have the legal status of a registered drug in Germany, whereas in other EC-countries and in the US they are used as health foods.

There are also recent clinical studies showing decreased bioavailability of digoxin, phenprocoumon, indinavir and ovulation-inhibitors after continuous

administration or coadministration, respectively, of hyperforin-rich St. John's wort extract (Yarsin®).

An activation of P-Glycoproteine (pGP) has been suggested to explain the results of the first digoxin-interaction study, in which the c_{max} showed a decrease whereas the elimination showed not much change (Johns et al. 1999); this was confirmed by experimental studies, in which hyperforin was shown to be the relevant constituent as a potent activator of the pregnane X receptor in liver cells (Moore et al. 2000) and in carcinoma cells (Wentworth et al. 2000).

An induction of CYP3A4 was observed in the rat, but has also been demonstrated in healthy volunteers after a 14-day administration of hyperforin-rich extract (Durr et al. 2000; Roby et al. 2000). On the contrary, no significant effect on CYP3A4 or 2D6 activity was seen in healthy volunteers comedicated with alprazolam or dextromethorphan (Markowitz et al. 2000). On the other hand, the inhibition of CYP3A4 in vitro enzyme-essay (Budzinski et al. 2000) and in microsomes (Obach 2000) could be misleading and might reflect an unspecific effect of surface-active ingredients of the plant.

An unpublished study with the hyperforin-free *Hypericum* extract Ze 117 showed that there was no significant effect to the serum levels of ethinylestradiol and 3-ketodesogestrol (personal communication Prof Braffström).

Available St. John's wort formulations in Germany show wide variety in respect to total daily dosage and amount of their constituents. There are various extracts, differing in concentrations, solution fluids und dosages, but there are also administrations with plant powder, fatty oil extracts, herbal teas and fresh

plant juices.

Therefore, we evaluated the interaction of digoxin and different formulations and/or doses of St. John's wort in a randomized, double-blind, placebo controlled parallel group study in 97 healthy volunteers in three study parts. The relative changes of digoxin trough levels and digoxin area under the curve after 14 days of comedication with St. John's wort were compared to placebo. Comedication with high-dose methanolic extract (L1160) and high dose encapsulated plant powder (4g daily dose) resulted in a similar reduction of digoxin trough level (19%) and digoxin AUC (25%, 27%) compared to placebo ($p < 0.05$). Comedication with 2g daily dose of encapsulated powder reduced digoxin trough level (13%) and AUC (18%) less pronounced; these changes seem not to be of clinical relevance.

By comedication with encapsulated powder with the same daily dose of hypericin, but almost no hyperforin, no interaction was observed. Lower daily doses (ig or 0.5g) of encapsulated powder, fatty oil formulation, tea or fresh plant juice did not indicate any interaction. Therefore, the interaction of St. John's wort is dose dependent and the degree of interaction is most likely related to the content of hyperforin. Low-dosed preparations used in self-medication seem not to exhibit relevant interaction potential. Further studies are planned with cyclosporin A to confirm the results.

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Table 1: Clinical studies on interaction of Hypericum extract (if not mentioned: hyperforin-rich, 900 mg)

Comedication Treatment duration/ Dosage	No. of volunteers/ patients	Results	Literature
Digoxin 14 d 0.25 mg	13 V (12) V	AUC 25% decrease Cmin 19/33% decrease	Johne et al. 1999
Phenprocoumon 1 d 12 mg 11th d	10 V Cross-over	AUC 17% decrease	Maurer et al. 1999
Amitriptyline 12 d 150 mg	12 Pat.	AUC 22% decrease 41% decrease Nortriptylin	Roots et al. 2000
Indinavir 1 d 2400 mg 14th d	8 V	AUC 57% decrease	Piscitelli et al 2000
- duodenal biopsy hyperforin-free extract 7 d	4 V	Induction of MDR1 and CYP3A4	Drewe et al. 2000
Cimetidine 7 d Carbamazepine 7 d	11 V 11 V	No interaction to Hypericum- kinetics	Donath et al. 2000
Carbamazepine 900 mg extract 14 d	8 V	No interaction	Burstein et al. 2000
Dextromethorphan Alprazolam	7 V	CYP 2D6 - no significant effect AUC 41% decrease CYP 3A4 - no significant effect	Markowitz et al. 2000
- (900 mg extract 14 d)	13 V	6 β hydrocortisol/cortisol increase (3A4 increase)	Roby et al. 2000
s.d. Digoxin (900 mg extract 14 d)	8 V	AUC 18% decrease PGP/MDR 140% increase CYP3A4 50% increase	Durr et al. 2000
Caffeine		No interaction	Gewurtz et al. 1999

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