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The antidepressant effect of hypericum perforatum extract Ze 117 is associated with reduced possibilities of drug interactions than hypericum perforatum extract LI 160.

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Hypericum perforatum (HP) is the most extensively investigated medicinal herbs with antidepressant effect. Differences showed by HP extracts in their antidepressant effect and their clinical consequence of HP-drug interactions have been related with HP extract different composition, particularly regarding to their primary ingredients hyperforin and hypericin content. Experimental data and clinical trials have shown that low-hyperforin-content HP has a comparable antidepressant efficacy in the treatment of mild/moderate depression (1) (2). However, hyperforin is responsible for CYP3A4 induction via activation of a nuclear steroid/pregnane and xenobiotic receptor (SXR/PXR) and hypericin is a P-glycoprotein inducing compound (3), which are the main origin of HP-drug interactions. Changes in cytochrome P-450 (CYP-450) activity could modulate the effect of different drugs. Some of the reported interactions are based on findings from in vitro studies but the clinical importance of which remain to be demonstrated. Two different hypericum extracts, Ze 117 and LI 160, which are differently composed, Ze 117 (0.15-0.25% hypericin, 0.5% hyperforin) and LI 160 (0.3% hypericin, 4-6% hyperforin) were checked regarding their antidepressant-like activity vs. classical antidepressants with and without liver CYP 450 enzyme activity modulation by cimetidine.
Experimental procedures followed the ECC Directives and were approved by local authorities. Male Wistar rats (n=6 per group, 6 months old, weight 314±25 g, Charles River-Spain) were injected (i.p. once a day) with Ze 117 (20 mg/kg, Zeller AG), LI 160 (20 mg/kg, Lichtwer Pharma AG), imipramine (IMI) (10.9 mg/kg, Novartis SL), fluoxetine (FLU) (5 mg/kg, Lilly and Dista) or saline (SAL), in presence and absence of cimetidine (CIM) (50 mg/kg, Rimsa) during 20 days. The forced swim test (4) was used for the evaluation of the antidepressant-like effect. The opend-field test was used for the evaluation of the motor activity. The total CYP 450 content of the liver was measure using spectrophotometry methods in liver microsomes.

Results are expressed as mean±sem and were compared by Student t test and ANOVA test followed by Bonferroni post-test.

The drugs antidepressant effect (reduction of the immobility time) ranking order was: i) without cimetidine's CYP-450 inhibition: IMI 109±33s >Ze 117 163±21s =FLU165±29s >LI 160 201±234s >SAL 224±17s, $p<0.05$; ii) with cimetidine's CYP-450 inhibition: IMI 113±27s >LI 160 144±13s >FLU 171±21s >Ze 117 188±10 >SAL 219±20s, $p<0.05$). The motor activity reduction ranking order was: IMI >LI 160 >Ze 117 >SAL, $p<0.05$). LI 160 significantly reduced the liver CYP-450 total content with respect to SAL (-43.3%, $p<0.05$) while Ze 117 had lower effect (-25.9%, $p<0.05$).

In conclusion, hypericum perforatum extract Ze 117 shows higher antidepressant effect and lower inhibitory effect of the total CYP 450 liver content than hypericum perforatum extract LI 160. Liver CYP 450 inhibition by cimetidine increased the antidepressant of LI 160 but did not modify the antidepressant effect of Ze 117.

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