Clinical Studies on St. John's wort (*Hypericum perforatum* L.)

Depression

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Hypericum Depression Trial Study Group, 2002	Major depression	R, DB, PC, MC n=340 adults with baseline total HAMD score ≥ 20	8–18 weeks	900–1,500 mg SJW/day or 50–100 mg sertraline/day or placebo; divided into 3 doses/day	LI 160 SJW extract standardized to between 0.12% and 0.28% hypericin; sertraline (Zoloft®)	Initial treatment phase = 8 weeks. Patients responding positively were given respective treatments for additional 18 weeks. On the 2 primary outcome measures neither sertraline nor SJW performed significantly differently from placebo, based on HAMD or CGI scale. Full response occurred in 31.9% placebo group, 24.8% sertraline group (p=0.26), and 23.9% SJW group (p=0.21). Sertraline was better than placebo on a secondary measure: a CGI improvement scale that included partial responders (p=0.02). Authors concluded that the study does not support the efficacy of SJW in moderately severe major depression, acknowledging the low assay sensitivity of this trial, and the fact that 35% of trials on known antidepressants result in failure.
Friede *et al.*, 2001	Mild to moderate depression	R, DB, MC n=240 (HAMD scores 16–24)	6 weeks	500 mg/day Ze 117 vs. 20 mg/day fluoxetine	Ze 117 vs. fluoxetine	SJW extract is equivalent in efficacy (p=0.09) to fluoxetine for both overall depressive symptoms and the main symptoms of depressive disorders. SJW is particularly effective in depressive patients suffering from anxiety symptoms. Tolerability for SJW revealed better safety (p<0.001) than for fluoxetine.
Shelton *et al.*, 2001	Severe depression	R, DB, PC, MC n=200 patients with baseline HAMD ≥ 20	SJW for 4 weeks (n=98) or placebo (n=102) for 8 weeks	900 mg/day increased to 1200 mg/day or placebo	SJW standardized extract (LI 160) or placebo	The number of patients with a remission of depression was significantly higher with SJW than placebo (p=0.2), but they had low rates 14.3% with SJW vs. 4.9% for placebo in the full intention-to-treat analysis. SJW was well tolerated, with the only adverse effect being headaches (41% vs. 25%). The random analyses for the HAMD, HAMA, CGI-S, and CGI-I showed significant effects for time but not for treatment or time-by-treatment interaction. The study concluded that SJW was not effective in treating major depression (no active control used).
Brenner *et al.*, 2000	Mild to moderate depression; comparison of SJW and selective serotonin reuptake inhibitors (SSRIs)	R, DB, C n=30	7 weeks	600 mg per day of standardized SJW extract or 50 mg per day of sertraline for 1 week, followed by 900 mg per day of SJW or 75 mg per day of sertraline	LI 160 vs. sertraline	Severity of symptoms, as measured by HAMD and the Clinical Gobal Impression scale was significantly reduced in both treatment groups (p<0.01). The difference in clinical response, based on reduction in HAMD for each group, was not statistically significant. SJW extract was found to be at least as effective as sertraline in treating mild to moderate depression.
Woelk, 2000	Mild to moderate depression without suicidal ideation (ICD-10)	R, DB, PG, MC (40 centers) n=324 HAMD scale >18. Mean HAMD 22.4 (SJW); 22.1 (imipramine) (ages >18 years)	6 weeks	250 mg SJW extract, 2x/day; 75 mg imipramine, 2x/day	Remotiv® (Ze 117) vs. imipramine	157 subjects on SJW had HAMD scores drop from mean or 22.4 at baseline to 12.00 at 12 weeks end, compared to 167 imipramine patients' scores of 22.1 dropping to 12.75 (no statistical difference between groups). CGI scores at end were mean of 2.22 of 7 for SJW group and 2.42 for imipramine group (no statistical difference between groups). In self-assessment, mean scores were 2.44 for SJW and 2.60 for imipramine (no statistical difference between groups). Tolerability scores were better for SJW (1.65) than drug (2.35); (no statistical difference between groups). Researchers concluded that SJW is therapeutically equal to imipramine for mild to moderate depression and tolerated better. This is largest trial on SJW comparing it to imipramine at standard dose (150 mg/day).
Philipp *et al.*, 1999	Moderate depression	R, DB, MC, PG, PC, Cm n=262	2 months	1050 mg/day SJW , 350 mg, 3x/day vs. daily dosing of 50 mg, 25 mg, then 25 mg (100 mg total/day) imipramine	STEI 300 vs. imipramine	SJW was more effective than placebo and as effective as 100 mg/day imipramine in the treatment of depression as measured by HAMD, HAMA, and Clinical Global Impression scales. Improved quality of life also demonstrated in Zung self-rating depression scale. Proven safe with less adverse effects than imipramine.

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Depression (cont.)

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Lenoir *et al*., 1999	Mild to moderate depression (ICD-10)	R, DB, PG, Cm, MC n =260 (over 20 years old)	6 weeks	1 tablet 3x/day (1 mg total hypericin/day or 33 mg total hypericin/day or 17 mg total hypericin/day)	Hyperiforce® tablets containing approximately 60 mg SJW extract (4–5:1) of shoot tips standardized to 0.33 mg total hypericin content/tablet (controls standardized to 0.11 mg or 0.055 mg total hypericin/ tablet)	At the end of the treatment period, a reduction of about 50% in Hamilton Depression scores was observed in all groups. No significant differences between dosages. SJW was determined to be effective in all 3 doses and is well tolerated.
Laakmann *et al*., 1998a	Mild to moderate depression	R, DB, PC, MC, PG n=145 (mean age, 51 years placebo; 48.7 years W5573 group; 47.3 years SJW group)	7 weeks	900 mg/day (300 mg, 3x/day)	WS 5573 (0.5% hyperforin) or WS 5572 (5% hyperforin) or placebo	Study demonstrated relationship between hyperforin dose and antidepressant efficacy. 5% hyperforin SJW product enhanced patients' quality of life by producing appreciable relief from symptoms compared to 0.5% (p=0.017) and placebo (p=0.004). No statistical difference between 0.5% and placebo. Study suggests hyperforin is a therapeutically active constituent with antidepressant activity.
Wheatley, 1997	Mild to moderate depression (DSM-IV)	R, DB, PG, MC n=156 (HAMD score between 17–24, mean score SJW=20.6 amitriptylline= 20.8) (ages 20–65 years)	6 weeks	900 mg/day SJW extract (300 mg, 3x/day) or amitriptyline (3x25 mg in a fixed dose manner)	LI 160 vs. amitriptyline	Comparable efficacy to amitriptyline with clear tolerability advantage. No statistically significant difference in response rate was shown between SJW and amitriptyline (p=0.064). In the CGI item "side-effects of drugs," greater tolerability for SJW was apparent (p<0.001 at week 2, p<0.05 at weeks 4 and 6).
Schrader *et al*., 1998	Mild to moderate depression	R, P, DB, PC, MC n=159	6 weeks	One, 250 mg tablets SJW extract 2x daily (1 mg hypericin daily)	Ze 117 SJW extract standardized to 0.5 mg hypericin/ tablet	Of SJW patients, 56% were deemed responsive to treatment compared to 15% on placebo. There were few adverse effects: 5 placebo, 6 SJW (mostly minor gastrointestinal upsets in SJW group). Researchers noted that the good tolerability profile contributed to the high compliance of the SJW group.
Vorbach *et al*., 1994	Typical depression with single episode, recurrent episode, neurotic depression, and adjustment disorder with depressed mood (DSM-III-R).	R, DB, Cm, MC n=130 (mean HAMD score: 20.2 SJW group; 19.4 imipramine group) (ages 18–75 years)	6 weeks	900 mg/day SJW extract (300 mg, 3x/day) vs. imipramine (3x25mg daily)	LI 160 vs. imipramine	SJW showed equal effectiveness to and better tolerability than imipramine. Improved HAMD total score by 56% on SJW and 45% on imipramine. SJW caused less frequent and less severe side effects than imipramine.
Harrer *et al*., 1994	Depression (ICD-10)	R, DB, Cm, MC n=102 (HAMD score >16) (ages 25–65 years)	4 weeks	900 mg/day SJW extract (300 mg, 3x/day), maprotiline, (25 mg 3x/day)	LI 160 vs. maprotiline	Showed roughly equal efficacy to maprotiline. No significant difference between groups on HAMD, D-S, and CGI scores (HAMD score >16). 25% in SJW group and 35% in maprotiline group reported adverse drug effects.

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Depression (cont.)

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Harrer and Sommer, 1994	Mild to moderate depression (ICD-9)	R, DB, PC, MC n=89 (HAMD score <20) (ages 20–64 years)	1 month	900 mg/day (300 mg, 3x/day)	LI 160 vs. placebo	Significantly (p<0.05) reduced depressive symptoms after 2 weeks and even further after 4 weeks (p<0.01) compared to placebo. No notable side effects were reported.
Hübner *et al*., 1994	Mild depression and somatic symptoms (ICD-09)	R, DB, PC n=39 (Mean HAMD score 12.55 SJW group, 12.37 placebo group) (ages 20–64 years)	4 weeks	900 mg/day (300 mg, 3x/day)	LI 160 vs. placebo	Significant reduction in HAMD score in SJW group compared to placebo (p<0.01). Final score=7.17. Significant reduction in falling asleep compared to placebo (p<0.01). Benefited patients with good tolerability and high compliance (p<0.05). By week 4, 5% statistical difference level in HAMD between placebo and SJW groups. No adverse effects reported.
Hänsgen *et al*., 1994	Major depression and temporary depressive neurosis (DSM-III-R)	R, DB, PC, MC n=72 (HAMD score >16) (ages 18–70 years)	6 weeks	900 mg/day (300 mg, 3x/day)	LI 160 vs. placebo	Significantly improved all 4 psychometric tests vs. placebo, with no serious side effects reported: Hamilton depression scale (p<0.001), depression scale of von Zerssen (p<0.001), complaint inventory, Clinical Global Impression Scale.

Fatigue and Seasonal Affective Disorder

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Stevinson *et al*., 1998	Fatigue	O, U, pilot n=20 (mean age, 44.4 years)	6 weeks	900 mcg/day hypericin (300 mcg 3x/day)	Kira®	Significantly lowered perceived fatigue after 2 weeks (p<0.05) and reduced significantly more after 6 weeks (p<0.01). Significantly (p<0.05) reduced mean scores of depression and anxiety.
Martinez *et al*., 1994	Seasonal affective disorder (SAD) (DSM-III-R) HAMD scale>16	R, SB n=20 (ages 29–63 years)	4 weeks	900 mg/day (300 mg, 3x/day)	LI 160 with bright light (3000 lux) vs. LI 160 with dim light (<300 lux)	Significant improvement in symptoms over time with SJW and bright light (p=0.001). No adverse drug reactions reported.

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Shüle *et al*, 2001	Effect of SJW on cortisol, growth hormone, and prolactin	R, PC, CO n=12 healthy males between 20 and 35 years old	5 hours	300 mg WS 5570, 600 mg WS 5570, or placebo	WS 5570 SJW extract or placebo	No prolactin stimulation was observed (p>0.05) in SJW or placebo. A small but statistically significant (p<0.05) increase in growth hormone occurred after 300 mg SJW. After 600 mg SJW, cortisol stimulation was clearly observed (p<0.05) from 30 to 90 minutes after application.
Schempp *et al*., 2001	Phototoxicity of SJW in treatment of depression (UV-B, UV-A, visible light, solar-simulated radiation)	R, P n=72	Single-dose or steady-state 7 days	Single dose: 6 or 12 coated tablets, 3x daily (containing 5400 or 10,800 mcg total hypericins). Steady-state trial: initial dose of 6 tablets (1800 mcg hypericins) followed by 3 x 1 tablets (2700 mcg) per day for 7 days	LI 160	No significant changes were observed (erythema and melanin index) in either the single or multiple doses administered, with the exception of a slight, (p=0.50) influence on UV-B-induced pigmentation. The authors concluded that this study did not indicate phototoxic potential in the oral administration of higher than therapeutic doses (2–4 times) of SJW for depression.

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Burnstein *et al*., 2000	SJW effects on steady state carbamazepine and carbamazepine-10,11-epoxide pharmacokinetics	U n=8	21 days	100 mg 2x/day for 3 days, then 200 mg, 2x/day for 3 days, then 400 mg 1x/day for 14 days; then 300 mg SJW with carbamazepine, 3x/day for 14 days	St. John's wort (0.3% standardized tablet) or carbamazepine (brand not stated)	The study concluded that SJW did not increase clearance of carbamazepine.
Taylor and Kobak, 2000	Obsessive-compulsive disorder (OCD)	O n=12 patients with 12 months diagnosis of OCD (DSM-IV)	12 weeks	450 mg SJW extract, 2x/day	450 mg SJW extract standardized to 0.3% hypericin (brand not stated)	Significant change from baseline, with mean change in Yale-Brown Obsessive-Compulsive Scale of 7.4 points (p=0.01). At end of trial, 5 patients were rated much or very much improved on clinician CGI, 6 were minimally improved, and 1 had no change. Side effects included diarrhea (3 subjects) and restless sleep (2 subjects). Improvements noted in first week. Results warrant placebo-controlled study of SJW for OCD.
Grube *et al*., 1999	Menopausal symptoms	O Drug monitoring study n=106 women 43–65 years old with symptoms characteristic of pre- and post-menopause	12 weeks	One, 300 mg tablet, 3x/day	Kira®	Self-assessment by Menopause Rating Scale for assessing sexuality and CGI. Psychological, psychosomatic, and vasomotor symptoms recorded at baseline, 5, 8, and 12 weeks. Significant improvement in psychological and psychosomatic symptoms. Menopausal symptoms reduced or disappeared in majority (76.4% by patient assessment; 79.2% by physician assessment). About 80% of women considered sexuality was improved with SJW
Czekalla *et al*., 1997	Electrocardiogram effects in patients with depression	R, DB, Cm, MC n=209	6 weeks	1,800 mg/day or 150 mg/ day imipramine	Jarsin® 300 vs. imipramine	SJW did not delay conduction through the atria or depolarization and repolarization in the ventricles. Imipramine increased heart rate and can cause pathological repolarization. High-dose SJW extract (i.e., 2x normal daily dose) produced fewer cardiac conduction defects than tricyclic antidepressants for treating elderly patients or patients with a pre-existing conductive dysfunction, and should be considered safer than tricyclic antidepressants, especially in patients with pre-existing conduction disorders.

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