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Evidence for St John's wort in the treatment of depression

440 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 3 St John's wort St John's wort (SJW), *Hypericum perforatum*, contains a combination of at least 10 different components, including hypericin, hyperforin and various flavonoids.¹ Preparations of SJW are often unstandardised and this has complicated the interpretation of clinical trials. Both the active ingredient(s) and mechanism(s) of action of SJW are unclear.¹ Constituents of SJW may inhibit monoamine oxidase (MAO), inhibit the reuptake of noradrenaline and serotonin, upregulate serotonin receptors and decrease serotonin receptor expression.¹ Some preparations of SJW have been granted a traditional herbal registration certificate,² but this is based on traditional use rather than proven efficacy and tolerability. SJW is licensed in Germany for the treatment of depression.²

Evidence for St John's wort in the treatment of depression A number of trials have examined the efficacy of SJW in the treatment of depression. They have been extensively reviewed³⁻⁷ and most authors conclude that SJW is likely to be effective in the treatment of mild to moderate depression.^{3,5,6,8} Cochrane concludes that SJW is more effective than placebo in the treatment of mild to moderate depression, and is as effective as, and better tolerated than, standard antidepressants.⁴ Some formal guidelines recommended its use in mild to moderate depression.⁹ The supporting evidence, however, is not without several limitations. For example, studies in German-speaking countries showed more favourable results than studies elsewhere.⁴ Concerns have also been raised about the inadequate dosing of SSRIs in comparative studies.^{10,11} In two reanalyses of data from a large negative RCT of SJW, both participant and clinician beliefs about treatment assignment were more strongly associated with clinical outcomes than the actual treatment received: those who guessed randomisation to active treatment fared better than those who guessed randomisation to placebo.^{12,13} Efficacy in severe depression remains uncertain.⁴⁻⁶ Oddly, there appear to be no published studies of SJW in depression since 2020,¹⁴ perhaps reflecting the difficulties inherent in marketing for a profit an unpatentable natural product. There

is a little evidence for SJW in postmenopausal depression¹⁵ or in pain syndromes.¹⁶ Other important observations include: ■ ■The active component of SJW for treating depression has not yet been determined. Trials used different preparations of SJW, most of which were standardised according to their total content of hypericins. However, evidence suggests that hypericins alone do not treat depression.⁵ ■ ■Many SJW preparations bought over the internet are sold as unregulated food supplements and are often of poor quality and/or are adulterated.² One analysis of 47 different SJW preparations found that 36% were adulterated with other *Hypericum* species and 19% were adulterated with food dyes.² ■ ■Published studies are generally acute treatment studies. There are only preliminary data to support the effectiveness of SJW in the medium term. Longer--term and relapse-prevention data are lacking.¹⁷ On balance, SJW should probably not be prescribed. We lack sufficient understanding of what the active ingredient is or what constitutes a therapeutic dose and most preparations of SJW are unlicensed.³

Depression and anxiety disorders CHAPTER 3 Adverse effects SJW appears to be well tolerated.^{5,6} In a systematic review of existing studies, adverse effects were significantly less common than with older antidepressants, slightly less than SSRIs and similar to placebo.⁶ The most common, if infrequent, adverse effects are nausea, rash, fatigue, restlessness and photosensitivity.¹⁸ Although severe phototoxic reactions seem to be rare, patients should be informed that SJW can increase light sensitivity.¹⁸ SJW may also share the propensity of SSRIs to increase the risk of bleeding; a case report describes prolonged epistaxis after nasal insertion of SJW.¹⁹ Case reports have also described mania, hypomania and mixed states associated with SJW.²⁰ Manic symptoms associated with SJW have been documented in patients both with^{20,21} and without previously recognised bipolar affective disorder.²⁰ The onset of manic symptoms ranged from 3 days to 2 months.²⁰ Caution is advised with high doses and those with a known history of bipolar affective disorder.²² A single case report documented supraventricular tachycardia associated with SJW.²³

Drug interactions SJW is a potent inducer of intestinal and hepatic CYP3A4, CYP2C9, CYP2C19, CYP2E1 and intestinal p-glycoprotein.^{18,24} Hyperforin is responsible for this effect.²⁵ The hyperforin content of SJW preparations varies 50-fold, which will result in a different propensity for drug interactions between brands. Preparations providing a daily dose of less than 1mg hyperforin are less likely to induce CYP enzymes.^{25,26} CYP3A4 activity is induced over 1-2 weeks and returns to normal approximately 7 days after SJW is discontinued.²⁷ SJW significantly reduces plasma concentrations of warfarin,²⁸ hormonal contraceptives,²⁹ digoxin and indinavir.¹⁸ According to case reports, SJW has lowered plasma concentrations of clozapine, theophylline, ciclosporin, gliclazide, rivaroxaban and statins.^{18,24,30-32} There is a theoretical risk that SJW may interact with some antiseizure medications. It has also been reported that SJW can increase the effects of clopidogrel (a pro-drug).²⁴ Serotonin syndrome has been reported when SJW was taken together with sertraline, paroxetine, nefazodone and various triptans.^{33,34} SJW should not be taken with any drugs that have a predominantly serotonergic action. Box 3.5 details the key points that patients should know about SJW. Box 3.5 Key points that patients should know about St John's wort

■ ■Evidence suggests that SJW may be effective in the treatment of mild to moderate depression, but we do not know enough about how much should be taken or what the adverse effects are. There is less evidence of benefit in severe depression. ■ ■SJW is not a licensed medicine. ■ ■Available preparations are not standardised and differ in potency.³ ■ ■SJW can interact with other medicine³ resulting in serious adverse effects. Some important drugs may be metabolised more rapidly and therefore become ineffective with serious consequences (e.g. increased viral load in human immunodeficiency virus, failure of oral contraceptives leading to unwanted pregnancy, reduced anticoagulant effect with warfarin leading to thrombosis). ■ ■The symptoms of

depression can sometimes be caused by other physical or mental illness. It is important that these possible causes are investigated. ■ ■It is always best to consult the doctor if any herbal or natural remedy is being taken or the patient is thinking of taking one.

Revision #1

Created 2026-01-04 20:15:04 UTC by Omar Ayman

Updated 2026-01-04 20:15:04 UTC by Omar Ayman