Complementary and Alternative Medicines: *Hypericum perforatum* (St John's wort)

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There is far less information about the effectiveness, safety and potential for interactions for complementary and alternative medicines (CAMs) compared to conventional medicines. There is no regulation of their quality or contents in New Zealand. Consider also other risks of CAMs, such as patients choosing them over conventional treatment, and the often substantial cost.
Report any possible adverse effects or interactions to CARM: www.nzphvc.otago.ac.nz

What is it?

St. John's wort (SJW) is a flowering plant native to Europe, which grows well in New Zealand. It has yellow, star-shaped flowers with five petals (1).

SJW contains at least 10 different components (2). Hypericin, pseudohypericin and hyperforin are the main active constituents and all have a half-life around 24 hours (1). There are no standardised preparations available in New Zealand. Plant extracts are not required to have the same quality control as medicines.

What do people use it for?

In New Zealand, SJW is commonly marketed for mood, stress, tension, worry and irritability. Other promoted uses include menopausal symptoms, premenstrual syndrome and irritable bowel syndrome.

Does it work?

A number of trials have examined the efficacy of SJW in the treatment of depression (2). A Cochrane review concluded that SJW was more effective than placebo in the treatment of mild to moderate depression, and was as effective and better tolerated than standard antidepressants (e.g. tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs)). However, efficacy in severe depression remains uncertain (3).

The mechanism of action for SJW's antidepressant effect is unclear. A variety of mechanisms have been suggested including the inhibition of the reuptake of noradrenaline and serotonin (2,4,5).

For depression a dose of 300 mg three times daily has been used in studies (equating to 2.7 mg hypericin per day)(6). The antidepressant effects shoud be apparent after 4-6 weeks (5).

SJW is possibly effective for improving the vasomotor symptoms of menopause (1,4). It is inconclusive if SJW is effective for anxiety, fatigue, cognitive function, premenstrual syndrome and sleep quality (6). It is ineffective for attention deficit hyperactivity disorder and irritable bowel syndrome (1,4,6).

Is it safe?

Adverse effects include nausea, rash, fatigue, restlessness, insomnia, anxiety and photosensitivity. Like the SSRIs it may be associated with an increased risk of bleeding (1,2).

Should women who are pregnant or breastfeeding take it?

Pregnancy: **Consider using an antidepressant with established safety data (e.g. SSRI or TCA).** From the limited information available, the use of SJW during pregnancy has not been associated with an increased risk of congenital malformations. A small study has reported individual cases of hypospadias, bilateral hip dislocation and heart septum defects in infants exposed to SJW in utero. Two case reports have described healthy pregnancy and neonatal outcomes following maternal use of SJW (7).

Breastfeeding: **Consider using an alternative agent.** The data on the safety of SJW in breastfeeding are limited. The weight adjusted maternal dose (WAMD) is 0.9-2.5%. Minor adverse effects such as colic, drowsiness and lethargy have been reported in infants exposed to SJW via breast milk (7).

Does it interact with medicines?

Yes. SJW induces multiple CYP enzymes (CYP3A, 2C19, 2C9 & 1A2) and P-glycoprotein (P-gp) and has been associated with treatment failures due to decreased plasma concentrations of the interacting drugs (see table below). The time to full induction, or recovery from induction following SJW cessation, is approximately 2 weeks. P-glycoprotein substrates are often also CYP3A substrates (8,9).

Pharmacokinetic interactions

Selected medicines	Elimination	Interaction with St John's wort
Anticoagulants/antiplatelets		
warfarin	CYP2C8/9	Induction of metabolism (CYP2C8/9), may ↓ INR.
dabigatran etexilate	P-gp	Induction of P-gp, may ↓[dabigatran]
rivaroxaban	CYP3A & P-gp	Induction of metabolism (CYP3A) & P-gp, may ↓ INR
clopidogrel (prodrug)	CYP2C19	↑metabolism to active moiety (CYP2C19), may ↑bleeding
Immunosuppressants	CYP3A	Induction of metabolism (CYP3A), may ↓efficacy
e.g. ciclosporin, tacrolimus	P-gp	Induction of P-gp, may ↓ efficacy
everolimus, sirolimus		Risk of transplant rejection
HIV protease inhibitors	CYP3A	Induction of metabolism (CYP3A), may ↓efficacy
e.g. indinavir, nelfinavir,	P-gp	Induction of P-gp, may ↓ efficacy
nevirapine, ritonavir,		Risk of HIV treatment failure
saquinavir		
HIV non-nucleoside reverse transcriptase inhibitors	CYP3A	Induction of metabolism (CYP3A), may ↓efficacy Risk of HIV treatment failure
e.g. efavirenz, nevirapine		
Anticonvulsants		
e.g. carbamazepine	CYP3A	Induction of metabolism (CYP3A), may
phenytoin	CYP2C8/9 & 2C19	↓[carbamazepine] Induction of metabolism (CYP2C8/9, 2C19), may↓[phenytoin]
Antiarrhythmics		
calcium channel blockers	CYP3A	Induction of metabolism (CYP3A), may ↓ efficacy
amiodarone	CYP3A	Induction of metabolism (CYP3A), may ↓ efficacy
digoxin	P-gp	Induction of P-gp, may ↓ [digoxin]
Statins	CYP3A	Induction of metabolism (CYP3A), may ↓efficacy
e.g. atorvastatin,		
simvastatin		
Oral contraceptives	CYP3A	Induction of metabolism (CYP3A), may ↓
e.g. oestradiol, desogestrel,		[contraceptive]
ethinylestradiol,		Risk of contraceptive failure
norethisterone		Additional methods of contraception advised
Clozapine	CYP1A2	Induction of metabolism (CYP1A2), may ↓ [clozapine]

Abbreviations: ↓ decrease, ↑ increase, [x] concentration of x, INR International Normalised Ratio

This is not an exhaustive list. Stopping, starting and changing brands of SJW may all affect the plasma concentration of other medicines.

Pharmacodynamic interactions

Serotonergic effects: Additive serotonergic adverse effects may occur when SJW is taken in conjunction with other serotonergic medicines e.g. antidepressants, some analgesics (e.g. tramadol) and anti-migraine agents (e.g. sumatriptan, rizatriptan). Signs of serotonin toxicity include confusion, delirium, agitation, restlessness, sweating and tachycardia.

Photosensitising effects: St John's wort is associated with photosensitivity, which can be additive with other photosensitising agents e.g. tetracyclines and cytotoxic drugs.

Switching

As a general rule of thumb a washout period of one week is reasonable when switching between a prescribed antidepressant and SJW and vice versa.

Key points

- When starting or stopping SJW check the patient's other medicines for potential interactions.
- The quality of available SJW preparations is unknown (the active ingredients may vary substantially between products and between batches of the same product).
- For a given indication, there are usually alternative therapeutic options with better data to support their use.

References

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