

HERBAL THERAPEUTICS

(2) DEPRESSION

By Jo Barnes, PhD, MRPharmS

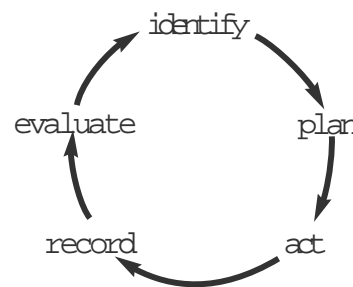
It has been estimated that one in five people will suffer from depression at some time during their lives. St John's wort is prescribable and some people may ask your advice on purchasing herbal remedies for depression. This article looks at the evidence for using herbal products to treat depression



identify gaps in your knowledge

1. What is the main constituent in St John's wort with evident antidepressant activity?
2. What types of depression can St John's wort be used to treat?
3. List three possible interactions between St John's wort and conventional medicines.

This article relates to the Royal Pharmaceutical Society's core competencies of "medicinal products" and "evidence-based practice" (see "Medicines, ethics and practice — a guide for pharmacists", number 25, July 2001, p104). You should consider how it will be of value to your practice.



Several herbs have traditionally been used in nervous system disorders. For example, oatstraw (*Avena officinalis*, *A sativa* L.), St John's wort (*Hypericum perforatum* L.) and vervain (*Verbena officinalis* L.) have been used as "nerve tonics" for "strengthening" the nervous system. However, with the exception of St John's wort, there has been little scientific investigation of the reputed antidepressant properties of these herbs.

It is beyond the scope of this article to consider the aetiology, types, diagnosis and treatment of depressive illness (see *PJ*, 24 February 2001, pp259–62 and *PJ*, 31 March 2001, pp433–42). Nevertheless, pharmacists are reminded that depression is a serious and potentially life-threatening condition. Pharmacists are encouraged, where possible, to probe discreetly individuals' reasons for purchasing St John's wort. If the intended use is depression, it is recommended that they apply usual protocols to establish the possible cause, duration and type of symptoms, treatments already tried or being used, other action taken, and so on. Particular consideration should be given to the potential for drug interactions, and St John's wort must not be taken with certain conventional antidepressants for this reason. In nearly all cases, individuals should be advised to seek support (eg, from family, friends, self-help groups etc) and to consult their general practitioner, particularly if symptoms do not improve. New cases of severe or major depression will require immediate referral.

ST JOHN'S WORT

St John's wort, also known as hypericum, is a herbaceous perennial plant native to Europe and Asia. The name St John's wort may have arisen because the flowers bloom around St John's day (June 24). The dried flowers, leaves and unopened buds are used medicinally.

St John's wort products have been among the top-selling herbal preparations in developed countries in recent years.¹ A small study

carried out in the United States identified that one of the main reasons for consumer use of St John's wort is the belief that it is more natural, safer and has fewer adverse effects than conventional antidepressants. Other reasons included ease of access and lack of effectiveness of conventional antidepressants.²

Major constituents Initially, hypericin (Figure 1) was considered to be the antidepressant constituent of St John's wort, although more recent experimental and clinical evidence has shown that hyperforin (Figure 2) is a major constituent required for antidepressant activity.³ More research is needed to find out whether or not hypericin contributes to this activity, but many products containing extracts of St John's wort are still standardised on hypericin content because hyperforin is thought to be relatively unstable.⁴ St John's wort also contains other biologically active constituents, such as flavonoids, and further research is needed to determine whether these contribute to its antidepressant effect.

Product quality The issue of variation between manufactured products, and the suggestion that evidence for efficacy and safety should be considered to be extract- or product-specific, were raised in the first article in this series (*PJ*, 8 June, pp804–6). Some products contain only dried plant material, whereas others contain concentrated, standardised extracts and are manufactured according to the principles of good manufacturing practice (GMP).

An analytical study which investigated eight St John's wort products marketed in the US found that their hyperforin content varied from 0.01 to 1.89 per cent, and that only two products contained more than 1 per cent hyperforin, the minimum concentration likely to be required for antidepressant effects.⁵ Similarly, hypericin content varied from 0.03 to 0.29 per cent and, for several products, the actual content did not correlate with that stated on the product, ranging from 57 to 130 per cent of the labelled quantity.

Evidence of efficacy in "mild-to-moderate depression" Evidence from randomised controlled trials (RCTs) indicates that preparations of St John's wort extracts are more effective than placebo, and possibly as effective as certain conventional antidepressant agents in

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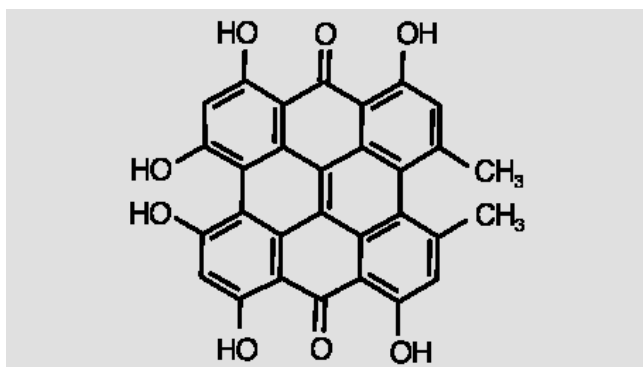


Figure 1: Chemical structure of hypericin, a naphthodianthrone

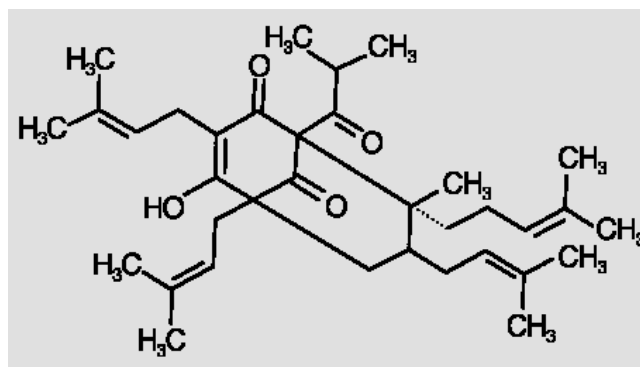


Figure 2: Chemical structure of hyperforin, a prenylated pfloroglucinol

treating the symptoms of mild-to-moderate depression.³ Generally, a few weeks' treatment is required before marked improvement is seen. Moderate depression is not necessarily suitable for self-treatment. In most of these trials, the Hamilton depression (HAM-D) scale was used to define depression (see Panel 1).

A Cochrane systematic review and meta-analysis included 27 RCTs of preparations of St John's wort extracts involving patients with "neurotic depression" and mild-to-moderately severe depressive disorders.⁶ The results of the meta-analysis showed that, overall, 300 to 1,800mg doses of St John's wort extract (hyperforin content unknown) over four weeks to three months were significantly superior to placebo (rate ratio 2.47; 95 per cent confidence interval 1.69–3.61), and as effective as some conventional antidepressants (rate ratio 1.01; 95 per cent confidence interval 0.87–1.16) such as amitriptyline and imipramine, in the short-term treatment of mild-to-moderately severe depressive disorders. However, for several reasons, such as the use of low doses of conventional antidepressants and small sample sizes in some trials, further trials comparing St John's wort preparations with conventional antidepressants were deemed necessary.⁶

Another meta-analysis used stricter inclusion and exclusion criteria. It included only six trials involving patients with depressive disorders defined by standard criteria (eg, the Diagnostic and Statistical Manual of mental disorders; DSM-III-R and DSM-IV) and the HAM-D scale was only used to measure clinical outcomes and not to define patient groups³ (see Panel 1). This meta-analysis also found that St John's wort extracts were superior to placebo ($n = 4$ trials) and as effective as tricyclic antidepressants ($n = 2$ trials), but concluded that further trials were still necessary to address methodological problems.

Both meta-analyses described above examined the effects of hypericin-standardised extracts of St John's wort. However, the total daily dose of hypericin varied between individual studies from 0.75 to 5.4mg, and the hyperforin content of the preparations tested was not documented, because most trials were carried out before it was

known that hyperforin is the more important constituent for antidepressant activity. Several new RCTs comparing St John's wort extracts with placebo and/or conventional antidepressants, including fluoxetine, in patients with mild-to-moderate depression have since been published.^{1,3,4} These new trials confirm the efficacy of certain St John's wort extracts over placebo, and provide some further evidence that St John's wort extracts may be as effective as some conventional antidepressants, but again, further studies are required to confirm this.

Evidence of efficacy in major depression St John's wort is neither recommended nor suitable for the treatment of patients with major depression. Nevertheless, some RCTs have investigated the effects of St John's wort extracts in such patients. A randomised, double-blind trial involving 200 patients with a baseline HAM-D score of at least 20 who received LI-160 (a hypericin-standardised St John's wort extract) 900 to 1,200mg daily, or placebo, for eight weeks found that at the end of the study, there was no statistically significant treatment effect ($P = 0.16$).⁷ Likewise, an intention-to-treat analysis showed that there was no difference between St John's wort and placebo in response rates at week eight (response rates and 95 per cent confidence intervals for St John's wort and placebo, respectively: 26.5 per cent, 18.7 to 36.2 per cent; 18.6 per cent, 12.1 to 27.5 per cent).

In a randomised, double-blind, three-arm trial, 340 patients with major depressive disorder were randomly allocated to treatment with LI-160 (hypericin content 0.12 to 0.28 per cent; hyperforin content 3.1 per cent) 300mg three times daily, sertraline 50mg daily, or placebo, for eight weeks.⁸ Doses of St John's wort and sertraline (or placebo equivalent) could be increased up to 1,500mg and 100mg daily, respectively, during the study. After eight weeks, there was no statistically significant difference between St John's wort and placebo, or between sertraline and placebo, on the two primary outcome measures (change in HAM-D score and the full response rate). Sertraline, but not St John's wort, was more effective than placebo on the clinical global impression scale, a secondary outcome measure (see Panel 1).

This study has been widely reported as evidence for the lack of efficacy of St John's wort in moderately severe depressive disorders. However, given that the established antidepressant sertraline also failed to demonstrate a statistically significant effect on the primary outcome measures, compared with placebo, there is also a view that the findings are inconclusive.

Mechanism of action The precise mechanism of action for the antidepressant effect of St John's wort is unclear. Studies involving small numbers of healthy male volunteers have indicated that St John's wort extracts may have dopaminergic activity and effects on cortisol, which may influence concentrations of certain neurotransmitters.^{3,4} Biochemical and pharmacological studies have suggested the following possible mechanisms:

- 1 Inhibition of synaptosomal uptake of serotonin (5-HT), dopamine and norepinephrine by St John's wort extract
- 1 Inhibition of synaptosomal uptake of serotonin, dopamine, norepinephrine, gamma-aminobutyric acid and L-glutamate by hyperforin

PANEL 1: GLOSSARY

DSM-IV is the most recent edition of the Diagnostic and Statistical Manual of mental disorders, a tool for professionals to classify mental disorders. Three types of depression (major depression, chronic depression and minor depression) are recognised and levels range from mild to moderate to severe.

The Hamilton depression scale is a 17-point screening instrument designed to measure the severity of depression. The points allow assessment of symptoms such as insomnia, mood, work capacity, anxiety, insight and agitation. Scores of 14–20 indicate mild depression and 21–25 indicate moderate depression.

The clinical global impression scale is a 7-point scale used to judge the progress (or not) of a disease when an intervention has been made. If the patient is deemed as "very much improved" a score of 1 is given. A score of 7 is given if the patient is seen to be "very much worse".

action : practice points

1. Are there sufficient warnings of interactions and cautions in or on the packaging of the St John's wort products you sell? Write a protocol for sale.
2. Visit the MCA website and obtain a copy of the St John's wort factsheet for health care professionals, which contains a table of clinically important interactions. Keep this for reference purposes. www.mca.gov.uk
3. Read the Hypericum Depression Trial Study Group trial.⁸ Do you agree with the findings? Do you need to look back at the previous two CPD articles about evidence based medicine?

evaluate

How could your learning have been more effective?
What will you do now and how will this be achieved?

1. Upregulation of 5-HT₂ receptors in rat brain by St John's wort extract^{1,3,4}

Some previous *in vitro* studies have suggested that St John's wort inhibits monoamine oxidase (MAO), although other studies fail to confirm this.^{1,3,4} Experimental studies involving animal models of depression provide supporting evidence for the antidepressant effects of St John's wort.^{1,3,4}

Adverse effects Data from RCTs and post-marketing surveillance-type studies indicate that standardised extracts of St John's wort, made to pharmaceutical quality standards, are generally well-tolerated when used at recommended doses for up to 12 weeks.³ Adverse effects reported are usually mild and include gastrointestinal symptoms, dizziness, confusion and tiredness.

A meta-analysis of RCTs comparing St John's wort with certain conventional antidepressants in depression indicates that St John's wort has a more favourable short-term safety profile and is associated with a lower frequency of adverse effects (26.3 per cent with St John's wort compared with 44.7 per cent with certain antidepressants).⁶ There are isolated reports of photosensitivity associated with St John's wort, due to the hypericin content.^{1,3,4} There are also isolated reports of mania and hypomania associated with the use of St John's wort by patients with various depressive disorders, although in each case there were other pharmacological factors and/or underlying illness which make an assessment of causality difficult.³

Pregnancy and lactation There are isolated reports of women who have taken St John's wort for limited periods during pregnancy.^{3,4} The excretion of hypericin and hyperforin into breast milk was investigated in a lactating woman who was taking St John's wort 300mg three times daily for post-natal depression.⁹ Low concentrations of hyperforin were found to be excreted into breast milk (< 0.50ng/ml). Given the lack of data, St John's wort should not be used during pregnancy and lactation.^{1,3,4}

Drug interactions There is a single report in the literature of a hypertensive crisis occurring in a man who had consumed cheese and red wine and who was reported to have been taking a St John's wort preparation for seven days previously.¹⁰ However, data from clinical trials and post-marketing surveillance studies do not provide any evidence to substantiate this report and at present, the consensus is that St John's wort does not have MAO inhibitory activity and the avoidance of foodstuffs containing tyramine and medicines containing sympathomimetic agents is not considered necessary.³

Concern has been raised over interactions between St John's wort preparations and some medicines, including anticonvulsants, ciclosporin, digoxin, HIV protease inhibitors, oral contraceptives, selective serotonin reuptake inhibitors, theophylline, triptans and warfarin.^{1,3,4} Patients taking these medicines should stop taking St John's wort, but only after seeking medical advice because dose

adjustment of the medicines concerned may be necessary (except in the case of oral contraceptives). Interactions between conventional drugs and herbal medicines will be discussed in detail in a future article.

DISORDERS RELATED TO DEPRESSION

The effects of LI-160 have been explored in preliminary studies involving individuals with seasonal affective disorder (SAD).^{3,4} Improvements in symptom scores were reported in participants who received St John's wort with or without light therapy. LI-160 has also been reported to improve symptoms of depression (and anxiety) in an open study involving women with premenstrual syndrome.^{3,4} However, these studies were not placebo-controlled, and further investigation is required before St John's wort can be recommended for these conditions. LI-160 is also under investigation in patients with somatoform disturbances (psychogenic symptoms resembling those of physical disease).

An RCT involving 27 patients with SAD who were randomised to receive a standardised ginkgo (*Ginkgo biloba*) leaf extract, or placebo, did not provide any convincing evidence that ginkgo was of benefit.³ However, the results cannot be considered definitive because of the small sample size and other limitations. Standardised extracts of ginkgo leaf have also been tested in open, uncontrolled studies involving patients with antidepressant-related sexual dysfunction. While relief of sexual dysfunction and improvements in "sexual stress" were reported, the study designs do not allow any definitive conclusions to be drawn.³

Good-quality products containing concentrated standardised extracts of ginkgo leaf are generally well-tolerated when used at recommended doses.³ Adverse effects are usually mild and include gastrointestinal symptoms, nausea, headache and diarrhoea. Rarely, allergic skin reactions occur. There are isolated reports of bleeding associated with ginkgo use, although a causal relationship has not been definitively established.^{1,3} Ginkgo has antiplatelet activity and should be avoided in patients taking anticoagulant and antiplatelet agents.³ The safety of ginkgo will be considered in more detail in a later article.

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