

SAINT JOHN'S WORT (*HYPERICUM PERFORATUM*). A BALM FOR HURT MINDS?

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In the Christian tradition, mental illness was regarded, in general, as the state of being possessed by a devil (or devils). This is well illustrated by the parable of the Gadarene swine (Gospel according to St. Luke, Chapter 8: verses 26 to 33). Jesus casts the devils out of the man who was tormented and 'they entered into the swine and the herd ran violently down a steep place into the lake and were choked'. The man recovered at once and went on his way rejoicing. As a consequence of this widely-held belief it was logical to wear charms (or amulets) to ward off demonic assault and possession. Certain plants also came to be regarded as effective, either at driving devils out or in preventing them entering into and taking possession of the soul. In the latter category one plant that was highly prized was St. John's wort, or *Hypericum perforatum*, as it came to be known in the Linnaean classification of the eighteenth century. The word *Hypericum* is derived from the Greek 'hyper' (above) and 'eikon' (the picture), as a result of the popular custom in which various species of this genus were hung above holy pictures to repel the devil.¹

Over the last 10-20 years the plant has received serious consideration as a possible treatment for mental depression and attempts are under way to characterise its main active principles and to determine how they influence the brain to produce their beneficial therapeutic effects.²

THE PLANT

The genus *Hypericum* belongs to the family *Clusiaceae* and contains approximately 370 species.¹ The plant has opposite leaves that are dotted with glands. Typical flowers bear five sepals; five yellow petals; and stamens collected into five bundles. Well known examples include *H. calycinum* (Rose of Sharon; Aaron's beard) from South East Europe, and *H. perforatum* (St. John's wort or the Klamath weed) from Northern Europe. In the latter the leaves appear peppered with small holes when held up to the light; hence the name *perforatum* (perforated).

'Common St. John's wort' (Figure 1) grows in woodland, grassland and hedgerows throughout Europe, except in the far north, where it is replaced by the similar imperforate St. John's wort (*H. maculatum*). The plant usually forms a colony with many rounded stems coming from a spreading underground root system. The flower stalks, petals, sepals, fruit capsules and leaves are all covered with black dots.

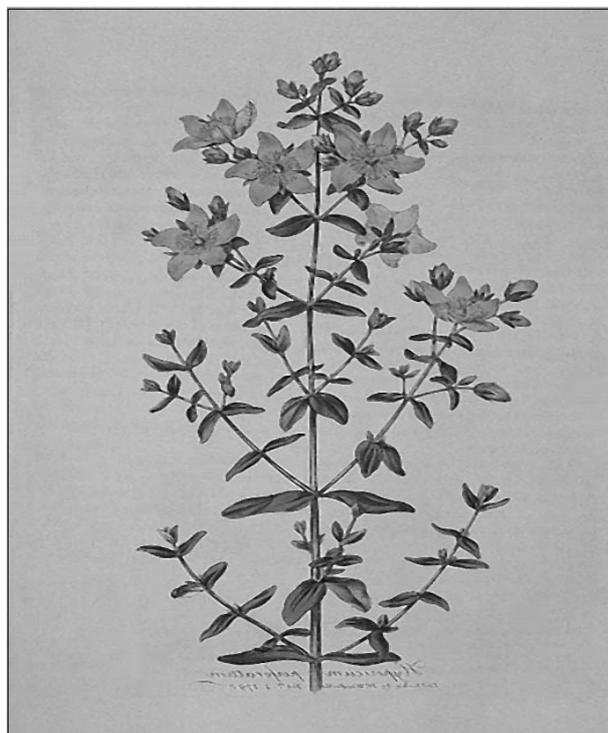


FIGURE 1
St John's wort (*Hypericum perforatum*).

THE HISTORY OF THE WORT OF ST. JOHN.

St. John's wort, St. John's wort.
My envy whoever has thee
I will pluck thee with my right hand
I will preserve thee with my left hand
Whoso findeth thee in the cattle field
Shall never be without kine.

Gaelic poem.³

The medicinal effects of the plant have been known for several thousand years and were mentioned by Hippocrates and Dioscorides. In pagan ritual, the flame-like buds were thought to signify the gift of fire from the gods. They were often burnt in the Beltane celebrations, on 1 May, in order to confer a celestial blessing on the sowing of the crops. Later in the year, at around the summer solstice, the 21 June, bundles of the plant were set alight and dragged across the fields to increase the yield from the crops.⁴ As has so often been the case, when Christianity was brought into Northern Europe, the new faith took over local customs and beliefs and changed them to its own purposes.

WHICH SAINT?

Several saints have competed over the years for their name to be associated with the plant but in the end St. John seems

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to have prevailed!

In Orkney the plant was known as 'St. Peter's wort'; in Gaelic the many names for the plant include the 'armpit package of Columba' and the 'Virgin Mary's herb'.³ It is believed that Saint Columba had a special affection for the plant because of its long traditional association with St. John the Evangelist and the Virgin Mary. Scots honoured the Evangelist on 6 May; the proximity to 1 May (the Beltane) may be more than coincidence. Moreover the Evangelist was the patron saint of Scotland until St. Andrew superseded him in the hagiological hierarchy.

Another St. John has also made a bid to name the plant, namely the Baptist (Figure 2). The flowers appear most profusely around the middle of June, and the 24th of that month is the feast of St. John the Baptist.⁵ In August red spots appear on the flowers and leaves, and these are said to symbolise the blood of the Baptist as he was beheaded in that month on Herod's orders.

A further interesting ritual has been described by the Reverend Hilderic Friend in relation to the plant.⁴ In the area around Hanover in Germany, on St. John's day, the people were known to go out in the morning and collect from *Hypericum* an insect that resembles a drop of blood.

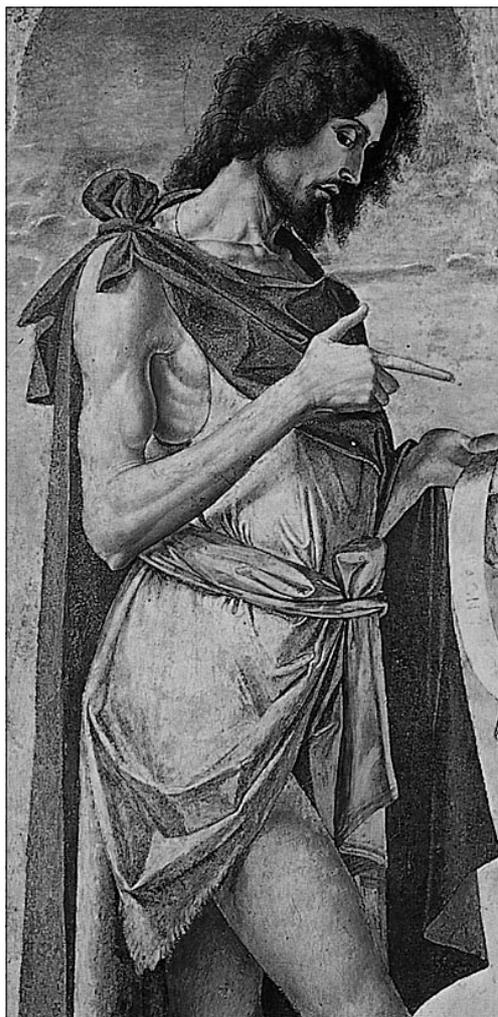


FIGURE 2
St. John the Baptist
(Alvise Vivarini; Gallerie Dell'Accademia Venice).

They believed that this insect *Coccus polonica*, had been created to keep alive the memory of the foul murder of the Baptist. It was common lore that the insect could only be met with on this day, but this would seem rather unlikely!

THE MIDDLE AGES

As a result of its association with the saints and its ability to repel or disperse demons, the plant came to be known as *Fuga demonum* (the Scourge of the Devil). In due course it was associated with wound healing; Gerard notes in his *Herbal* in 1597 that St. John's wort is 'a most precious remedy for deep wounds, those that are through the body or any wound made with a venomed weapon.' He recommends that the leaves, flowers and seeds be stamped or pressed, immersed in olive oil and set in the hot sun when they will make an oil the colour of blood. He also says that the oil will 'provoke urine and be right good against the stone in the bladder'. This recommendation for wound treatment led to it being called in different parts of Great Britain 'Touch-and-Heal', and 'Balm of the Warrior's Wound.' These uses hark back to Pliny who had proposed it for the treatment of snake-bite and to Dioscorides who had used it as a febrifuge.

All manner of ailments and conditions were supposed to respond to *Hypericum* including bronchitis, haemorrhoids, burns, ulcers and urinary infections and it had truly become a panacea. In North America it is thought that a related *Hypericum* was used by the Iroquois tribe for fever treatment (and as a reproductive aid), and by the Cherokee for diarrhoea, venereal sores and snake-bite. This is an interesting example of the emergence of common traditions in widely separated cultures.

Lightfoot⁶ summed up the situation in Scotland at the end of the eighteenth century.

The superstitious carry this plant about with them as a charm against the effect of witchcraft or enchantment. It is esteemed as a wound healer (vulnerary); as a worm killer (vermifuge); to resolve coagulated blood and to promote urine.

As a consequence of the widespread use of the plant from Russia to Germany to Britain in the Middle Ages, it was also suggested that it helped minds 'disordered by various distempers'. Perhaps it relaxed wounded warriors. Herbalists in the nineteenth and twentieth centuries recommended the plant for depression, mania, anxiety and fatigue, without any definite scientific support for this usage.

THE GERMAN CONNECTION

Herbalists in Germany were particularly enthusiastic in the use of *Hypericum* and were said to have 'kept the flame of St. John's wort burning'. Known in that country as 'Johanniskraut' it was prescribed widely for nervous disability of all kinds. Many physicians in Germany still use herbal medicines like *Hypericum* as a first preference in depression: they resort to the synthetic tricyclics and serotonin-uptake-inhibitors only when St. John's wort appears to have failed.

As a result of the widespread use of the plant in Germany and many published reports, the government thought it right to investigate. Accordingly in 1978, it gathered together a group of experts (known as commission E) to investigate the matter and to report on the various

preparations that were available.⁷ They concluded that *Hypericum* was indeed effective in mild and moderate depression and that the active principle was most likely to be hypericin (Figure 3). As a result of this positive endorsement, the use of St. John's wort grew in popularity in Germany and in 1994 almost three million doses of it were prescribed for depression which, even if only 50% of these doses were taken (a conservative estimate), still represents a staggering level of use.

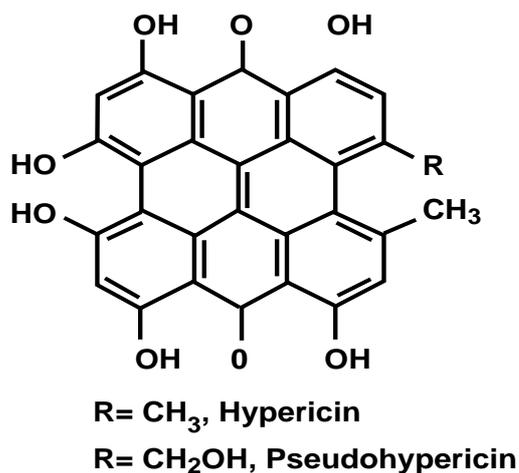


FIGURE 3

The chemical structure of Hypericin and Pseudohypericin.

STANDARDISATION OF THE HERBAL PREPARATIONS

One of the difficulties that has stood in the way of St. John's wort and its development is the wide variation in the extracts taken from the plant. In order to meet this problem, Lichtwer Pharma introduced a high-strength preparation in 1992 containing 300 mgm of hypericin per capsule or tablet. The extract is assayed and then adjusted so that it uniformly contains 0.3% of hypericin which is thought to be one of the main active principles. With this carefully standardised extract, it has been possible to conduct trials in the United Kingdom and America which in general have supported the earlier German work. The setting of such standards is a very definite advance but, as I shall point out below, the plant contains many other active compounds, some of which may be more important than hypericin (in terms of antidepressant activity). *Hypericum* is widely available in the United Kingdom as tablets, tinctures and ointments from retail and mail order sources.

PANDORA'S BOX

The major problem with herbal preparations, apart from standardisation, is the multiplicity of active compounds present in varying concentrations in leaves, stems and flowers.⁸ Any or all of these compounds could be effective against depression. Moreover one compound could act either to potentiate or inhibit the effect of another. There will be no substitute for tedious and painstaking controlled clinical trials of the pure chemical entities to attempt to resolve the continuing therapeutic dilemmas.

Compounds that have been isolated from the plant, and identified, include the following: hypericin,

pseudohypericin, hyperforin, biapigenin, 2-methylbutanol and gamma-amino butyric acid (GABA). These compounds have been described variously as having sedative; antidepressant; antibacterial and antiviral activity. Recently *Hypericum* was also claimed to contain melatonin which is regarded as one of the natural sleep hormones.⁹

HYPERICUM IN THE TREATMENT OF DEPRESSION

In 1996, *Hypericum* came to the attention of the official medical establishment in Great Britain, some 30 years later than it had in Germany. In an editorial in the *British Medical Journal*, De Smet and Nolan review St. John's wort as an active antidepressant.¹⁰ This editorial is based on a meta-analysis by Linde and colleagues of trials of *Hypericum* in depression (published in the same issue).¹¹ De Smet and Nolan concluded that they were in no doubt that St. John's wort was an effective antidepressant in mild to moderate cases but then raised several caveats. First, the number of properly controlled trials reported was limited. Second, entry criteria and rating scales (such as Hamilton's) had not been applied uniformly. Further it had been widely assumed that hypericin was the active principle and, indeed, asked for more evidence on this point (see below). They also suggested trials lasting longer than six weeks, trials in severely depressed patients, and they wanted also an estimate of the risk of relapse in patients who require long-term treatment.

It was also noted, that in line with other antidepressants, hypericin has to be taken for two to four weeks before it begins to elevate the mood but the plant extract appears to be well tolerated. In an open study of over 3,000 patients side-effects were few.¹² Those reported most commonly were nausea, vomiting and diarrhoea (0.6%); allergic reactions (0.5%) and fatigue (0.4%). Photosensitivity was not recorded specifically in this series of patients.

Since this editorial was published in 1996, some of the problems raised by De Smet and Nolan have been addressed. Verbach *et al* (1997) reported on a trial of St. John's extract in severe depression: hypericin (1,800 mgm of hypericin a day) was compared with 150 mgm of imipramine daily.¹³ The response of the patients was measured on the Hamilton Depression Score. Both regimens proved very effective over the six-week period of the trial and their individual efficacy could not be distinguished statistically. However *Hypericum* was associated with fewer adverse events. They suggested further trials in severe depression.

Wheatley (1997) from the Royal Masonic Hospital, reported on another recent comparative trial.¹⁵ He compared *Hypericum* with amitriptyline. In terms of efficacy, both medications were useful but there was a tendency for amitriptyline to produce a better response rate though this trend did not reach statistical significance. Perhaps the most striking feature of the trial relates to the reports of adverse events. Sixty-four per cent of patients on amitriptyline reported such events whereas only 37% on *Hypericum* did so. Wheatley concludes that the better tolerance of *Hypericum* may confer improved long-term patient compliance.¹⁴

It had been assumed for a number of years, on the basis of the work reported from Germany, that hypericin (Figure 3) was the active principle of St. John's wort; however, evidence is now gathering that would dispute this view. Hyperforin, a phloroglucinol derivative which is another ingredient in this plant is now a serious contender (Figure 4): it is a major constituent of the lipophilic fraction of the

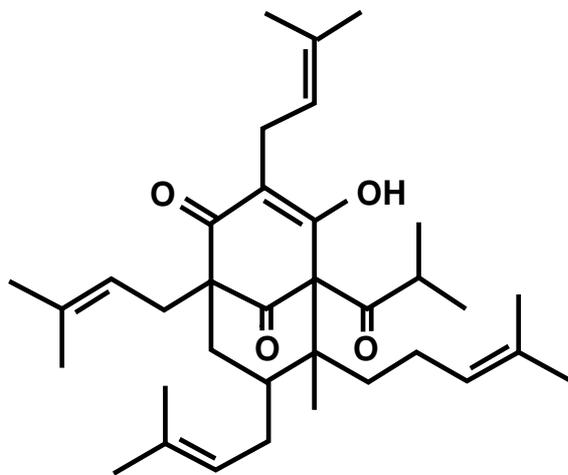


FIGURE 4
The chemical structure of Hyperforin.

plant and has been shown in vitro to be a powerful reuptake inhibitor of three neurotransmitters, serotonin (5-HT), dopamine and noradrenaline.¹⁵ In two animal models of depression, behavioural despair and learned helplessness, Chatterjee *et al* demonstrated also that the biological activity of *Hypericum* extracts correlated closely with the chemical content of hyperforin.¹⁵

Laakmann and co-workers studied¹⁶ 147 patients with mild to moderate depression (DSM-IV criteria); the patients were randomised respectively either to placebo, or to *Hypericum* extract with 0.5% hyperforin content, or to *Hypericum* extract with 5% hyperforin. The trial lasted for six weeks and the patients were assessed using generally accepted rating scales. Hyperforin 5% was significantly better than placebo ($p = 0.004$ Mann-Whitney) whereas the 0.5% group could not be distinguished from the control. These results suggest strongly that hyperforin (not hypericin) may be responsible for the antidepressant pharmacological activity of St. John's wort. This important result needs to be confirmed in other trials which use pure synthetic hyperforin and hypericin.

TOXICITY AND PHOTOTOXICITY OF HYPERICUM.

The other side of the therapeutic coin is toxicity. The evidence available is, in general, reassuring. In the meta-analysis referred to earlier, six comparative trials were compared with standard anti-depressants for drop-out rate.¹¹ With St. John's wort the mean drop-out rate was 0.8% and for the standard antidepressants 3.0% (a clear difference). The most common side-effects described in many studies are gastrointestinal (nausea, vomiting and diarrhoea) in about 0.55% of the total patients in the study.

The second most commonly reported side-effect is allergic and involves the skin. Hypericin (Figure 3) is a photosensitising compound and may therefore cause the patient to develop skin erythema when exposed to the sun. In one trial in Germany, where individuals took twice the recommended dose of hypericum (600 mgm three times a day rather than 300 mgm three times a day), about half of

the volunteers that were evaluated developed reddening of the skin.¹⁷ The erythema disappeared within a few days of stopping the administration of the extract. Individuals with fair skin appear to be more sensitive to the photosensitising effect as might be expected. No other adverse reactions were noted in this trial.

Katzenstein in his short monograph on St. John's wort reports that cattle in the Western United States have been particularly severely affected by this photosensitivity'.¹⁷ As a consequence it had been suggested that a flea beetle (*Chrysolina quadrigemina*) should be imported from Australia to control the weed biologically. The farmers have now, ironically, changed their minds and are growing *Hypericum* as a cash crop!

Finally, a rare toxic reaction to *Hypericum* should be described.¹⁸ In 1998 Bove reported the case-history of a 35-year-old woman who took 500 mgm of St John's wort a day after reading an article in a magazine. Within four weeks of this therapy she developed stinging pain in her face and on the back of the hands, provoked by light touch, air movement and cooling. There was no motor or other sensory abnormalities but a diagnosis of toxic neuropathy was made and the herbal preparation stopped. Partial recovery occurred in three weeks and this was complete in about two months. Bove suggested that *Hypericum* was activated by light on the skin of this patient and the resultant cytotoxic singlet oxygen and free radicals produced attacked the myelin sheath of peripheral nerves.¹⁸ At this stage of development of the herb it is essential that patients who develop unusual reactions should be carefully investigated.

OTHER POSSIBLE THERAPEUTIC USES OF HYPERICUM

St. John's wort was used by the ancients as a 'vulnerary', that is a wound-healing agent. The isolation of hypericin, and its capacity to generate free radicals on photo-activation, suggests a rationale for the primitive belief and its time honoured use. Preliminary work in the last decade suggests that healing of burns is accelerated, that *Escherichia coli* can be inactivated, and that certain viruses can be killed. Trials of hypericin and its derivatives are also under way in glioblastoma multiforme and malignant melanoma.

CONCLUSION

In Shakespeare's *Macbeth* (Act II Scene 2: lines 40-41) the distraught Thane of Cawdor pleads for sleep with the words 'Balm of hurt minds; great nature's second course'. Patients with depression and anxiety often exhibit early morning waking or difficulties in going to sleep, and crave that 'peace that passes all understanding'. St. John's wort may prove such a balm for hurt minds but there are a number of important unresolved problems. Can an active principle be isolated from its Pandora's box? Is the herb also active in severe depression? What is the relapse rate when it is compared with tricyclic antidepressants and specific serotonin reuptake inhibitors?

The final and perhaps most intriguing puzzle is how did ancient man (or woman) recognise St. John's wort as a sovereign remedy for wounds and the mind. We can only hazard a conjecture and suggest trial and error. The infusion of the plant into oil produced a red, blood-coloured, solution which suggested a use for bleeding wounds. Thus the armpit package of St. Columba might have given rest and sleep to minds disordered by sepsis or fever: it would then be but a small step to its use for minds possessed by demons.

At all events, the long story of St. John's wort from pagan times through to the Christian medieval period is a fascinating one. Let us now hope that the medicinal chemist and the clinical pharmacologist of the present day will generate the solid body of evidence required for a modern derivative to be employed widely. St John's wort will then be able to justify, finally, its distinguished medieval title of the Devil's scourge, *Fuga demonum*, and enable us to drive out the melancholy demons of the twenty-first century!

ACKNOWLEDGEMENT

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