ST JOHN'S WORT

Hypericum perforatum L.

Family

Hypericaceae, the St. John's wort family.

Parts Used

Herb.

Description

St. John's wort is a sprawling, perennial flowering herb native to Europe but has naturalised throughout much of the world's temperate regions including Australia, Asia, Africa and North and South America. It thrives in poor soils and is commonly found in meadows, fields, waste areas, roadsides, abandoned mines and quarries where it grows up to 1.2 metres in height. The stems and branches are densely covered by leaves which are covered in minute translucent spots, or oil glands, that are evident when held up to the light. These "perforated" leaves give the plant its species name. The upper portions of mature plants can produce several dozen five petaled yellow flowers, often with small black dots along their edges and numerous prominent stamens. Flowering occurs mostly during late spring and summer. The crushed flowers produce a reddish-purple pigment. Henriette Kress of www.henriettes-herb.com, one of the oldest herbal websites, says "A red colour from yellow flowers? If that's not magic, I don't know what is." By late summer the flowers produce capsules that contain dozens of tiny, dark brown seeds. Due to concerns over phototoxicity to livestock St John's wort is listed as a noxious weed. While stock animals tend to avoid grazing on it, if it is a dry year they will eat it to survive. It is regarded as a

significant environmental weed in Victoria and as an environmental weed in the ACT, New South Wales, South Australia and Western Australia. In Tasmania the importation or sale of St. John's wort plant is prohibited and measures to reduce, eradicate or restrict it to a particular area may be required. In the 19th century St John's wort was first introduced to Australia from Europe for ornamental and medicinal purposes. Many weedy infestations of a narrow-leaf form in eastern Australia can be traced to a garden planting near Bright, Victoria, in about 1880. The presence of a broader-leaf variety of St. John's wort in central New South Wales suggests a separate introduction to that area around 1890. Infestations in South Australia appear to have originated from plants cultivated in the Adelaide Botanical Gardens in 1859.[1,2,3,4]

Traditional Use

St John's wort was traditionally used for damaged nerve endings however over the past 30 years it has become a poster herb for depression and mood disorders, especially seasonal affective disorder, as well as holding promise as a therapy for cancer, inflammation, bacterial and viral infections.[5] This has resulted in a multi-billion dollar market for St. John's wort based products that consists of more than 13% of the total herbal supplement trade in Europe and approximately six billion USD worldwide.[6] Studies show that St. John's wort appears to be as effective as antidepressants in treating mild to moderate depression. It also appears to be better tolerated with fewer side effects.[7] While antidepressant is one of St. John's wort's actions there are many more valuable and important uses of this sunny herb. Passionate and practical American herbalist, Rosalee de la Forêt, emphasises that while modern science is racing to market the "one" herb (or constituent) for depression, herbalists are keen to recognise that herbs are best chosen for the particular person and not the disease.[8]

St. John's wort has been used since ancient times in Europe and was often associated with the magical world of fairies, witches and saints. St. John's wort was named by early Christians in honour of John the Baptist because they believed it released its blood red oil on August 29, the anniversary of the saint's beheading. The Greeks and Romans believed that St. John's wort protected against witches' spells. Christians adopted this pagan belief burning the herb on bonfires on St. John's Eve, June 23, to purify the air, drive away evil spirits and ensure healthy crops.[9]

One of the typical customs for the popular northern hemisphere celebrations of Midsummer and St. John's Day (June 24) includes the gathering of St.John's wort because the bright yellow flowers, which distinctly bear a great resemblance to the summer sun, bloom around St. John's Day and summer solstice. In ancient European pagan cultures priests and healers believed herbs attained the peak of their medicinal value on this day when the sun has reached its zenith in the sky. Interestingly, the actions of St. John's wort also bear strong correspondences to the sun. It is predominantly a warming remedy and it makes sense that it would be a primary remedy for melancholy and depression. American herbalist Matthew Becker states, "it brings a lot of the energy and warmth of the sun into your own body... it actually can warm your psyche".[10]

Constituents

Naphthodianthrones (including the red pigment hypericin and pseudohypericin). Flavonoids, mostly hyperoside, rutin, quercitrin, isoquercitrin, quercetin and kaempferol, phenolics, including hyperforin, procyanidins, essential oil, sterols (beta-sitosterol), vitamins C and A, xanthones and choline.[11]

Clinical Note

It has generally been considered that most of the pharmacological activities of St. John's wort are attributed to hypericin and the flavonoid constituent, hyperforin. In fact these two compounds have emerged as the most important for not just evidence based herbal medicine (not traditional herbal medicine) but also the pharmaceutical industry. Since large scale synthetic production of these compounds is prohibitively expensive St. John's wort extracts remain the main source of these two compounds.

Hypericin is the primary constituent responsible for the photosensitivity reactions reported with high intakes. Hyperforin is considered the main constituent responsible for inducing the cytochrome P-glycoprotein and thereby producing drug interactions (see below in Drug Interactions). However the most recent possible hypothesis to

explain the antidepressant activity in particular is that it might be due to multiple bioactive compounds contained in St. John's wort. In other words researchers suggest that the interplay of hyperforin, hypericin and some yet undefined flavonoids mostly account for the observed clinical efficacy of St. John's wort extracts.[12,13,14]

Recent scientific research has revealed that there is a loss of therapeutic efficacy upon isolation of a single constituent as compared with the whole, in other words the total extract is the active constituent. This notion of chemical synergy is illustrated in St. John's wort research. As mentioned above, recently researchers have said positive evidence of antidepressant effects had been found with St. John's wort whole plant preparations. The scientists said the efficacy of St. John's wort is "obviously defined by a range of parallel mechanisms of action, triggered by different constituents. The overall effect cannot be attributed to a single constituent or fraction (for example, hyperforin or hypericin). St. John's wort is therefore an outstanding example of the total extract being defined as the active constituent of herbal medicines." In 2018 Italian researchers said "The extract (St. John's wort) as a whole has to be considered as the active substance since several groups of active compounds contribute to its antidepressant efficacy. Nevertheless, manufacturers continue to describe St. John's wort extract as 0.3% hypericin without standardising the presence of the other active fractions. Hypericin is unlikely to be the sole active, or even the active." An earlier Cochrane review of St. John's wort says much the same thing: "Standardisation of a product on a defined component does not resolve the problem of preparations differing considerably (when used in research) as currently the exact mechanism for the antidepressant effects of St. John's wort extracts is still unclear and available research indicates that several components are relevant".[15,16,17]

To illustrate this further, components in St. John's wort previously considered void of activity have also been identified as important for pharmacological activity. For example, both procyanidin B2 and hyperoside increase the oral bioavailability of hypericin by 58% and 34%, respectively, and therefore, its clinical effects. Another report demonstrated that an extract devoid of both hyperforin and hypericin still exhibited antidepressant activity.[18]

The Herbal Extract Company specialise in manufacturing full-spectrum liquid St. John's wort as nature intended.

Actions

Anti-inflammatory, nervine tonic, relaxing nervine, nervous system trophorestorative, anxiolytic, antidepressant, vulnerary, alterative, antiviral, astringent, hepatic, antiproliferative, antispasmodic, anodyne.

Pharmacological Activity

This is not an exhaustive list. A small selection of recent human clinical studies are included in this monograph for brevity.

Antidepressant Activity

The existing evidence base indicates that St. John's wort is a herbal alternative to antidepressant medication, with fewer adverse events, without compromising effectiveness in symptom improvement in mild and moderate depression. In 2016 a systematic review of St. John's wort for major depressive disorder was conducted with 35 studies, examining 6,993 patients, meeting inclusion criteria. The available evidence suggests that St. John's wort is effective in treating patients with mild and moderate major depressive disorder compared to placebo and comparable to antidepressants. The observed adverse events were fewer than compared to antidepressants, however, adverse event assessments were limited. It has been estimated that approximately one in 30,000 people using St. John's wort will experience an adverse reaction, including those attributed to drug interactions. The incidence of side effects to St. John's wort is approximately 10-fold lower than for synthetic antidepressants.[19,20]

In patients suffering from moderate depression a daily dose of three 300mg St. John's wort tablets was significantly superior to the selective serotonin reuptake inhibitor (SSRI) antidepressant paroxetine (20mg). After six weeks of treatment significantly more patients treated with St. John's wort responded to treatment and more patients

showed remission compared with the reference group. The results of this recent double-blind, randomised trial confirm and strengthen the results of earlier studies. Due to these findings St. John's wort may be considered as first line treatment for patients with mild to moderate depressive episode. The 64 participants treated with St. John's wort showed a reduction in depression severity scores. To give readers an idea of how standardised tablets are made the standardised St. John's wort tablet was a stabilised dry extract 3 to 7:1 and used 80% methanol as the extraction solvent. It was standardised to 3 to 6% hyperforin, 0.1 to 0.3% hypericin, not less than 6% flavonoids and not less than 1.5% rutin. The high remission rate is of importance as more than 50% of patients with major depression will eventually relapse, a predictor of which is incomplete remission, and therefore there is a strong need for continued antidepressant therapy to maintain the remission period. Evidence so far suggests that St. John's wort can be successfully applied for prophylactic continuation treatment in patients prone to relapse after recovery from an acute episode of depression without an increase in the number of adverse events. The researchers noted that these results cannot be easily transferred to other St. John's wort extracts or clinical trials as the indication, composition and quality can greatly vary across products. They said only a minority of St. John's wort extracts have been tested in randomised, double-blind, controlled clinical trials. As the quality and therapeutic suitability of each product may depend on the chosen manufacturing process, each of these products needs its own clinical proof of efficacy. This is extremely important to remember when comparing studies as variations in chemical composition could be responsible for differences in results.[21]

Treatment with St. John's wort is an efficient way of reducing hot flushes, menopausal symptoms and depression in postmenopausal women a 2019 randomised controlled trial found. The study was conducted on 80 postmenopausal Iranian women, aged between 45 to 60. Forty women received 270 to 330mcg tablets of St. John's wort and forty women received placebo. The dose was given three times a day for two months. The frequency and intensity of hot flushes, and intensity of depression, significantly decreased in the St. John's wort group compared to the control group. At the end of the study 80% of women in the intervention group did not have depression compared to only 5.7% in the control group.[22] An earlier systemic review assessing the effects of black cohosh for the treatment of menopausal vasomotor symptoms concluded that black cohosh improved overall symptoms by 26%. St. John's wort appeared to complement the effects of black cohosh so using them together may be useful.[23]

Additionally St. John's wort was found to improve libido when used to treat seasonal affective disorder and improved sexual wellbeing in 80% of perimenopausal women when prescribed for psychosocial symptoms.[24]

Research suggests that St. John's wort may help relieve physical and emotional symptoms of premenstrual syndrome (PMS) in some women including cramps, irritability, food cravings and breast tenderness. The results of a randomised, double-blind, placebo-controlled, human clinical trial showed that daily use of the St. John's wort was more effective than placebo for the most common physical and behavioural symptoms associated with premenstrual syndrome. This may be due to St. John's wort's ability to restore liver function, its known effect on the nervous system and its ability to mildly reduce cramping.[25]

St. John's wort may assist in smoking cessation. In a recent Australian open label study investigating the efficacy of St. John's wort, nicotine patches and combination St. John's wort/nicotine patches for smoking cessation the St. John's wort treatment (500mcg tablet twice daily containing 1.375g St. John's wort and 500mcg hypericin) significantly reduced the amount of craving over the 10 weeks of treatment compared to the other two treatments. The 60 volunteers had been smoking for at least five years and were smoking at least 10 cigarettes per day.[26]

Antiviral Activity

Antiviral herbs elicit a direct immune response against viruses. Many studies have shown that St. John's wort has antiviral activity and can have a considerable effect against cytomegalovirus (in the herpes virus family) and human immunodeficiency virus. It was considered highly effective against influenza A virus in preclinical studies but more

human clinical trials need to be done to fully understand its therapeutic effects. St. John's wort is indicated where Graves' disease is suspected to be caused by a viral infection. Graves' disease typically presents with nervousness, insomnia and irritability.[27]

Topical Activity

A 2017 double-blind, placebo-controlled, pilot study showed that St. John's wort ointment could decrease redness, scaling and thickness in patients with mild to moderate plaque psoriasis. The researchers said St. John's wort's efficacy is probably related to its effect on lowering cytokines including tumour necrosis factor-alpha (TNFα). TNFα is known to directly contribute to the characteristic plaque covered in silvery scales through induction of keratinocyte proliferation.[28]

Indications

- Mild to moderate depression and to reduce the risk of relapse, anxiety, stress, burnout, exhaustion, chronic fatigue syndrome (where there is a viral infection with concomitant depressive symptoms), seasonal affective disorder, premenstrual syndrome, perimenopausal and menopausal women with psychological symptoms, anxiety and depression associated with irritable bowel syndrome
- Nerve pain, nerve entrapment in osteoarthritis, sciatica, fibromyalgia, migraine headaches
- Gastrointestinal conditions such as oesophagitis and peptic ulcers, liver stagnation
- Viruses including herpes viruses such as cold sores and shingles, Graves' disease (caused by virus)
- Topically to treat burns, injuries, allergic dermatitis, psoriasis, muscle pain, bacterial vaginosis

Energetics

Neutral (can be warming and cooling), drying. Taste is slightly bitter, pungent, sweet.[29]

Use in Pregnancy

In practice St. John's wort is not recommended in pregnancy.

Contraindications

Some people, particularly fair skinned people, find that taking St. John's wort (especially hypericin standardised extracts) causes photosensitivity although this is unlikely at therapeutic doses. While this is true for livestock such as cows, horses, pigs, sheep and goats it is unusual for this to happen with full spectrum St. John's wort preparations in humans. In fact ironically sometimes the infused oil is used to protect the body from sunlight and to soothe sunburn. Nevertheless people taking St. John's wort internally, or applying it externally, should avoid artificial light such as tanning beds. St. John's wort should not be used concurrently with other photosensitising drugs (e.g. retinoids, a group of medications related to Vitamin A).

Drug Interactions

According to Rosalee de le Forêt if St. John's wort is famous for depression, it is probably equally infamous for its known effects on pharmaceutical drugs. It increases the metabolic pathways used by many prescribed drugs thus reducing blood levels of these drugs which may lead to loss of therapeutic effect and potentially render them ineffective.[30]

St. John's wort is one of the few herbal medicines that has been subjected to controlled studies in order to determine the significance of its interaction with numerous drugs, which are mainly due to CYP450 enzyme induction in the liver and the induction of P-glycoprotein. This may result in a reduction in the plasma concentrations and therapeutic effects of medicines metabolised by these enzymes. High dose St. John's wort and several chemical substances, including warfarin and cyclosporin, have been described in some of the first case reports of herb-drug interactions in the literature and nowadays belong to the most well-known examples for herb-drug interactions.[31]

St. John's wort is contraindicated with multiple pharmaceutical medications listed below although the list is not exhaustive. The actions of many other drugs depend on their route and rate of metabolism and thus other drugs may also interact with St John's Wort. It is important to note that when patients stop taking a preparation containing St. John's wort, plasma concentrations of interacting medicines may rise and result in toxicity. In general

the following medicines are not likely to interact with St.John's wort: topical medicines with limited systemic absorption (inhalers, skin creams and ointments, eye and ear drops, enemas etc) and non-psychotropic medicines (any medication which does not primarily treat mental illnesses) which are principally excreted renally (e.g. antibiotics, diuretics).[32]

New safety data and evidence is constantly emerging, so it is imperative that practitioners investigate other sources, and do extensive research, to find out whether there are any new known safety concerns or interactions when prescribing St. John's wort for patients already taking pharmaceutical medicines. The clinical significance of many interactions is still unpredictable because of the variable chemical composition of products. Precaution should be exercised when prescribing ANY herbs to a patient on powerful drugs with a narrow dose range between efficacy and toxicity. It is said that in fact most natural products (herbs and food) can interact with prescribed drugs.[33,34]

Clinically Important Interactions of St John's Wort

(Patients taking drugs listed below should not start taking St. John's wort preparations):

Anticonvulsants (sold under the brand names clonazepam, phenobarbitone (barbiturate) and phenytoin, among others and used in the treatment of epileptic seizures, as mood stabilisers in bipolar disorder, borderline personality disorder and neuropathic pain): St. John's wort may increase drug metabolism resulting in reduced drug efficacy and risk of seizures. Avoid concurrent use unless under medical supervision so that doses may be altered appropriately.[35]

Antidepressents (Selective serotonin reuptake inhibitors (SSRIs) and related drugs such as citalopram, fluoxetine (Prozac), fluvoxamine (for obsessive-compulsive disorder), paroxetine, sertraline (Zoloft) and nefazodone): Potential for serotonergic syndrome with concurrent use. St John's wort may decrease tricyclic drug plasma levels and also may increase available serotonin. Avoid if possible or use only under close medical supervision.[36]

Antihistamines (to relieve allergy): A clinical study demonstrated the potential for St John's wort to decrease drug levels. Monitor patient.[37]

Antivirals (e.g. Tamiflu): Avoid concurrent use.[38]

Barbiturates (central nervous system sedative hypnotics found in sleeping pills): Avoid concurrent use.[39]

Benzodiazepines (minor tranquilisers or sleeping pills such as Valium (diazepam), Xanax (alprazolam) and Restoril (temazepam) commonly used in short-term management of anxiety disorders, specifically panic disorder or generalized anxiety disorder): A clinical study demonstrated reduced drug levels with concurrent midazolam and St John's wort use. Avoid concurrent use unless under medical supervision. Drug dosage modification may be required.[40]

Bronchodilators (Used for asthma treatment. Known as Seretide and Symbicort among others): Case reports show herb can decrease serum levels. Avoid concurrent use.[41]

Cardiac glycosides (such as digoxin used for heart failure and irregular heartbeat): Reduced blood levels and loss of control of heart rhythm or heart failure. A clinical study demonstrated that St John's wort significantly decreased serum levels of digoxin within 10 days of concurrent use. Avoid concurrent use.[42]

Chemotherapeutics (such as doxorubicin, vincristine and prednisone, also known as cytotoxic agents, used to treat or cure cancer): Clinical studies have shown St John's wort may decrease drug levels resulting in poor clinical outcomes. Avoid concurrent use.[43]

Contraceptives (birth control pills): Reduced blood levels with risk of breakthrough bleeding. Possible contraceptive failure. Breakthrough bleeding has been reported in 12 cases which is suggestive of reduced drug effectiveness. Reports from Britain and Sweden suggest unwanted pregnancies have occurred with concurrent use. Avoid use with low-dose oral contraceptive pill (OCP) (< 50mcg of oestrogen) if possible. Weigh the benefits of continuing St. John's wort against possible reduced contraceptive efficacy.[44]

Drugs of dependence: St John's wort may decrease serum levels of methadone. Avoid concurrent use.[45]

Human immunodeficiency virus (HIV) non-nucleoside reverse transcriptase inhibitors (antiretroviral drugs used in the treatment of HIV such as efavirenz, nevirapine and delavirdine): Reduced blood levels with possible loss of HIV suppression.[46]

Hormone medication: Decreased drug efficacy of hormone replacement therapy or OCP is possible.[47]

HIV protease inhibitors (a class of antiviral drugs that are widely used to treat HIV/AIDS and hepatitis C such as indinavir, nelfinavir, ritonavir and saquinavir): Reduced blood levels with possible loss of HIV suppression.[48]

Hypolipidemics (cholesterol lowering drugs such as the statins simvastatin, pravastatin and lovastatin): St. John's wort increases the metabolism of simvastatin and therefore drug dosage modification may be required.[49]

Immunosuppressants (antirejection drugs such as tacrolimus, cyclosporine, prednisone): Reduced blood levels with risk of transplant rejection. Case reports suggest it may reduce drug effectiveness. Avoid concurrent use.[50]

Theophylline (a class of drugs known as xanthines used to treat lung diseases such as asthma and chronic obstructive pulmonary disease (bronchitis, emphysema) to prevent wheezing and shortness of breath): Reduced blood levels and loss of bronchodilator effect.[51]

Triptans (Serotonin receptor agonists for migraine headaches such as sumatriptan, naratriptan, rizatriptan and zolmitriptan): Increased serotonergic effects with increased chance of adverse reactions.[52]

Warfarin (blood thinner): Reduced anticoagulant effect and need for increased warfarin dose. Reduced blood levels of warfarin have been noted in case reports from concurrent administration of St. John's wort. Avoid concurrent use.[53]

Administration and Dosage

Liquid Extract:	1:1
Alcohol:	60%
Weekly Dosage:[54]	15 to 80mL

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