Herba Hyperici

Definition

Herba Hyperici consists of the dried flowering tops or aerial parts of *Hypericum perforatum* L. (Clusiaceae) (*1–3*).

Synonyms

Hypericum officinarum Crantz, *Hypericum officinale* Gater ex. Steud., *Hypericum vulgare* Lam. (*4*). Clusiaceae is also referred to as Guttiferae or Hypericaceae.

Selected vernacular names

Balsana, bassan, bossant, common St John's Wort, corazoncillo, dendlu, devil's scourge, echtes Johanniskraut, Eisenblut, erba di San Giovanni, flor de sao joao, fuga daemonum, hardhay, Hartheu, herbe à mille trous, herbe de millepertuis, Herrgottsblut, Hexenkraut, hierba de San Juan, hiperico, hipericon, houfarighoun, iperico, Jageteufel, Johannisblut, Johanniskraut, John's wort, Jottannesort, klamath weed, Konradskraut, Liebeskraut, Lord God's wonder plant, Mannskraft, millepertuis, pelicao, perforata, perforate St John's wort, pinillo de oro, quian-ceng lou, St Jan's kraut, St John's Wort, seiyouotogiri, sint janskruid, tenturotou, Teufelsflucht, Tüpfelhartheu, witches's herb, zwieroboij (*2*, *4–7*).

Geographical distribution

Indigenous to northern Africa, South Africa, South America, Asia, Australia, Europe and New Zealand, and is naturalized in the United States of America (*2*, *7*, *8*). The plant material is harvested at flowering time (*1*).

Description

A herbaceous, aromatic perennial plant, up to 1 m high; glabrous throughout, green or sometimes glaucous. Stems rounded, 2-winged, erect and branched at top. Leaves oval, linear-oblong, broadly elliptic, subcordate, flat or more or less revolute-marginated with pellucid glands and sometimes a number of brown-black glandular dots. Flowers numerous, forming a broadly paniculate, compound cymose inflorescence. Petals oblong to oblong-elliptic, inequilateral with numerous glandular dots. Seed 1 mm long, cylindrical, brown, minutely pitted longitudinally (*2*, *8*, *9*).

Plant material of interest: dried flowering tops or aerial parts

General appearance

Stem glabrous greenish-yellow to brownish-yellow branching, 2-winged, cylindrical with 2 equidistant longitudinal bands. Leaves glabrous, generally sessile, opposite, greenish-grey, oval, 8–35 mm long, with entire margins; laminal margin often more or less revolute-marginated. Brown-black glandular dots sometimes present along the edges; numerous pellucid glands on the entire surface. Flowers, 2 cm in diameter, regular, forming a broadly paniculate, compound cymose inflorescence at top of stem, composed of: 5 green, lanceolate sepals, containing punctiform, black glandular dots on the edges; 5 golden-yellow petals, with numerous glandular dots along margins; and 3 staminal blades, each divided into multiple golden-yellow stamens. Anthers with single, terminal, dark pigment dot. Ovary elongated and conical, parietal placentation, carries 3 styles. Fruits trilocular capsules containing numerous brown, triangular seeds (*1–3*, *9*).

Organoleptic properties

Odour: weak, aromatic, balsamic; taste: bitter, acrid (*9–11*).

Microscopic characteristics

Transverse section of the stem circular and presents 2 lateral edges corresponding to the 2 longitudinal bands. From the exterior inwards are seen: epidermal layer formed of large polygonal cells; continuous collenchymal layer, slightly more developed at the 2 lateral edges; a cortical parenchyma containing crystals of calcium oxalate in the shape of a sea urchin; a ring of continuous phloem, distinct from the xylem, which consists of large vessels and a lignified parenchyma with a visible cambium; and a lacunose medullary parenchyma. Secretory pockets, almost invisible, rarely present in the endoderm. Upper surface of leaf section shows polygonal cells with sinuous, slightly beaded, anticlinal walls; cells of lower surface smaller, anticlinal walls more wavy with frequent paracytic, sometimes anomocytic, stomata; smooth cuticle, thicker on upper surface; straight-walled, elongated epidermal cells of veins occasionally beaded. Dorsoventral surface of leaf consists of a single palisade layer and large oil glands. Midrib shows single, collateral bundle with small area of lignified xylem. Microscopic characteristics of the sepal resemble those of the leaf. Petal narrow, elongated, thin-walled, epidermal cells with straight anticlinal walls on outer surface and wavy on inner surface. Stamen lignified fibrous layer of anther wall; elongated, thin-walled cells of filament with striated cuticle. Pollen grains spherical or elliptical, 20–28 µm in diameter, with 3 germinal pores and smooth exine. Ovary small polygonal cells

with underlying oil glands. Seed testa brown, thick-walled hexagonal cells (*2*, *3*, *9*).

Powdered plant material

Yellowish-green or brownish-green. Leaf fragments abundant, most containing large characteristic hypericin oil glands with brown to red contents. Fragments of leaf epidermis, the adaxial side with thick-walled punctate, slightly sinuate cells, and abaxial side with sinuate cells and paracytic stomata; mesophyll fragments with large secretory pockets which are spherical, bright, containing strongly refractive oil droplets; fragments of palisade parenchyma; stem fragments with reticulate spiral vessels, areolate punctation, long fibres with thick walls, ligneous parenchyma, and small number of thick-walled, characteristically punctate medullary cells; fragments of petals made of elongated rectangular cells with irregular nodulous thickenings, containing numerous yellow droplets and large, round to oval secretory pockets; fragments of anthers; pollen grains 20–28 µm in diameter, smooth spherical or elliptical with 3 germinal pores; clusters of calcium oxalate crystals (*1*, *2*).

General identity tests

Macroscopic and microscopic examinations and thin-layer chromatography for the presence of characteristic compounds (hypericin, pseudohypericin, chlorogenic acid, hyperoside) (*1*, *9–11*). Additionally, a liquid chromatography–mass spectrometry method is available (*12*). The presence of hyperforin and rutin in Herba Hyperici is used to differentiate *Hypericum perforatum* from other *Hypericum* species (*2*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Foreign organic matter

Not more than 3% stems with a diameter greater than 5 mm (*1*) and not more than 2% other foreign matter (*1*, *3*).

Total ash

Not more than 7% (*1*).

Acid-insoluble ash

Not more than 2.5% (*9*).

Sulfated ash

Not more than 2.5% (*9*).

Water-soluble extractive

Not less than 12% (*9*).

Loss on drying

Not more than 10% (*1*, *3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests

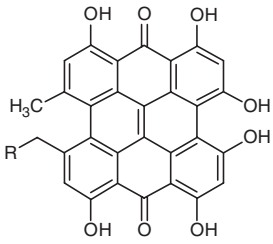
Chemical and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

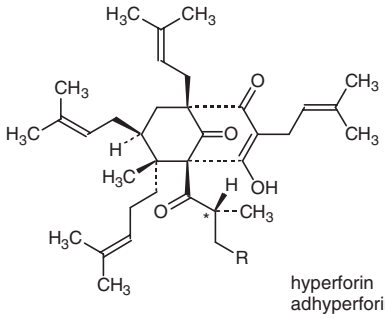
Contains not less than 0.08% hypericins calculated as hypericin, as determined by spectrophotometry (*1*). Quantitation can also be obtained by high-performance liquid chromatography (*2*, *16*).

Major chemical constituents

The major characteristic constituents include 0.05–0.30% naphthodianthrones (hypericin, pseudohypericin, hyperforin, adhyperforin); 2–4% flavonoids (hyperoside, quercitrin, isoquercitrin, rutin); and 7–15% catechin tannins (*2*, *4*, *7*, *17*). The structures of the representative constituents are presented below.

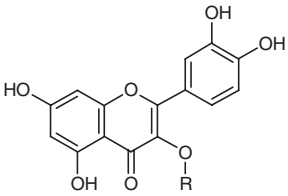


hypericin R = H
pseudohypericin R = OH

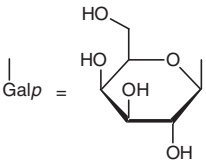


and epimer at C*

hyperforin R = H
adhyperforin R = CH_3

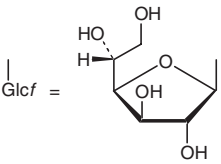


quercitrin R = Rha*p*
hyperoside R = Gal*p*
isoquercitrin R = Glc*f*
rutin R =Rha*p*-(1→6)-Glc*p*



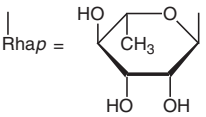
Gal*p* =

β-D-galactopyranosyl



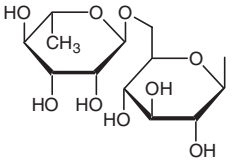
Glc*f* =

β-D-glucofuranosyl



Rha*p* =

6-deoxy-α-L-mannopyranosyl



Rha*p*-(1→6)-Glc*p* =

O -6-deoxy-α-L-mannopyranosyl-(1→6)-β-D-glucopyranosyl

Medicinal uses

Uses supported by clinical data

Symptomatic treatment of mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in the *International statistical classification of diseases and related health problems, Tenth revision (ICD-10) (18)*) (*19–31*).

Uses reported in pharmacopoeias and in traditional systems of medicine

Externally for the treatment of minor cuts, burns and skin ulcers (*8*, *32*). Topically for viral infections (*33*).

Uses described in folk medicine, not supported by experimental or clinical data

As an antiphlogistic agent in the treatment of inflammation of the bronchi and urogenital tract; treatment of biliary disorders, bladder irritation, the common cold, diabetes mellitus, dyspepsia, haemorrhoids, neuralgia, migraine headaches, sciatica and ulcers (*5*, *8*). Also used as a diuretic, an emmenagogue and an antimalarial agent (*5*, *8*).

Pharmacology

Experimental pharmacology

Antidepressant activity

Behavioural studies, performed primarily in rodents, have demonstrated the antidepressant activity of Herba Hyperici by measuring the exploratory and locomotor activities of animals in an unknown environment (*34*, *35*). Intragastric administration of a 95% ethanol extract of the herb to male gerbils (2 mg/kg body weight) suppressed clonidine-induced depression. Intragastric administration of the extract to male mice (5 mg/kg body weight) enhanced exploratory activity in a foreign environment and significantly prolonged narcotic-induced sleeping time in a dose-dependent manner; the treated mice also exhibited reserpine antagonism. Similar to standard antidepressant drugs, the extract (6 mg/kg body weight) increased the activity of mice in the waterwheel test following a single dose; prolonged administration (6 mg/kg body weight, daily for 3 weeks) decreased aggressiveness in socially isolated male mice (*35*). Intraperitoneal administration of a 50% ethanol extract of the herb to mice (250 mg/kg body weight) reduced the tail flick response to radiant heat, and significantly decreased swimming time in the forced swimming test ($P < 0.05$) and walking time on a rotating rod ($P < 0.005$), as well as exploratory activity ($P < 0.05$) (*36*). Significant, dose-dependent, antidepressant activities were observed in the behavioural despair test and the learned helplessness paradigm in rats treated intragastrically with a carbon dioxide extract of the crude drug containing 38.8% hyperforin (30 mg/kg body weight) or an ethanol extract containing 4.5% hyperforin (300 mg/kg body weight) ($P < 0.001$). The results were comparable to those obtained following intraperitoneal administration of imipramine (10 mg/kg body weight) (*37*). Intragastric administration of an ethanol extract containing 4.5% hyperforin (50, 150 and 300 mg/kg body weight, daily for 3 days) or a carbon dioxide extract devoid of hypericin but containing 38.8% hyperforin (5, 15 and 30 mg/kg body weight, daily for 3 days) had similar antidepressant activity in rodents (rats and mice) (*38*, *39*). In the same dosage range, the ethanol extract potentiated dopaminergic behavioural responses, whereas these effects were either absent or less pronounced in rodents treated with the carbon dioxide extract. In contrast, serotoninergic effects of the carbon dioxide extract were more pronounced than those of the ethanol extract (*38*). Intragastric administration of a methanol extract contain-

ing both hypericin and pseudohypericin (500 mg/kg body weight) to mice produced a dose-dependent increase in ketamine-induced sleeping time and also increased body temperature. The extract also decreased immobility time in the tail suspension test and forced swimming tests, which are both regarded as indicative of antidepressant activity (*40*). Intragastric administration of a 50% ethanol extract of the herb prolonged pentobarbital-induced sleeping time (13.25 mg/kg body weight) and depressed the central nervous system in male mice (25.50 mg/kg body weight). The observed effects were similar to those seen in mice treated with diazepam (2 mg/kg body weight) (*41*). Measurement of some metabolites of biological amines in the urine of various animal models has established a correlation between the excretion in the urine of 3-methoxy-4-hydroxyphenylglycol, the main metabolite of noradrenaline, with the start of the therapeutic antidepressant activity (*42*).

A hydroalcoholic extract of the herb inhibited serotonin (5-hydroxytryptamine, 5-HT) receptor expression in mouse brain synaptosome preparations in vitro (50 µmol/l), and similar effects were observed during ex vivo experiments (*43*). In other studies, hydroalcoholic extracts of the herb inhibited serotonin reuptake (IC_{50} 6.2–25.0 µg/ml) (*44*, *45*), and inhibited both γ-aminobutyric acid (GABA) reuptake (IC_{50} 1 µg/ml) and GABA type A receptor binding (IC_{50} 3 µg/ml) in vitro (*46*).

A hydroalcoholic extract of the fresh flowers and buds of *H. perforatum* (containing 0.1% hypericin) was subjected to a series of assays involving 39 receptor types and two enzymes. Receptor assays exhibiting at least 50% radioligand displacement or 50% inhibition of monamine oxidase (MAO) were considered to be active. The extract demonstrated specific affinity for the GABA (types A and B), serotonin, benzodiazepine and inositol triphosphate receptors, non-specific affinity for adenosine receptors and inhibited MAO types A and B. Purified hypericin lacked any significant MAO (type A or B)-inhibitory activity at concentrations up to 10 µmol/l, and had affinity only for *N*-methyl-D-aspartate (NMDA) receptors in rat forebrain membranes (*47*).

An ethanol extract of the herb inhibited radioligand binding to the NMDA, GABA type A and GABA type B receptors (IC_{50} 7.025, 3.240 and 3.310 µg/ml, respectively). The extract also inhibited synaptosomal GABA and L-glutamate uptake in vitro (IC_{50} 1.11 and 21.25 µg/ml, respectively) (*48*).

A methanol or carbon dioxide extract of the herb, and pure hyperforin significantly inhibited synaptosomal uptake of serotonin, noradrenaline, dopamine, L-glutamate and GABA in vitro (*49*). The carbon dioxide extract (containing 38.8% hyperforin) was more active than the methanol extract (containing 4.5% hyperforin), due to the higher hyperforin concentration. Inhibition was most pronounced with purified hyperforin, showing the following order of affinity: noradrenaline ≥ dopamine > GABA ≥ serotonin >> glutamate (IC_{50} 0.043–0.445 µg/ml) (*49*, *50*). Neither hyperforin nor the carbon dioxide extract inhibited the activity of MAO type A or B at concentrations up to 50 µg/ml (*49*).

A methanol extract of dried *H. perforatum* flowers inhibited radiolabelled-flumazenil binding to the benzodiazepine sites of the GABA receptor in rat brain

preparations in vitro (IC_{50} 6.83 µg/ml) (*51*). The number of serotonergic 5-HT_1 A and 5-HT_2 A receptors significantly increased in the brains of rats treated with an ethanol extract of the herb (2.7 g/kg body weight) daily for 26 weeks, whereas the affinity of both serotonergic receptors remained unaltered. These data suggest that prolonged administration of the extract induced upregulation of the 5-HT_1 A and 5-HT_2 A receptors (*52*). The affinity of hypericin for 30 types of receptor and reuptake sites was determined in vitro. At 1 µmol/l, hypericin inhibited less than 40% specific radioligand binding at all sites tested, except binding at the acetylcholine and sigma receptors (*53*).

The mechanism of the antidepressant effect of Herba Hyperici is not well understood. Early studies focused on the inhibition of MAO and catechol-*O*-methyltransferase (COMT), the two enzymes responsible for the catabolism of biological amines, such as serotonin. Initial investigations analysed the in vitro inhibition of MAO using a series of xanthones isolated from extracts of the herb (*54*, *55*). In later studies, hypericin was reported to inhibit MAO type A (IC_{50} 6.8×10^{-5} mol/l) and type B (IC_{50} 4.2×10^{-5} mol/l) in rat brain mitochondria in vitro (*56*). However, analysis of the hypericin fraction used in these experiments revealed that at least 20% of the extract was composed of other constituents, including some flavonoid derivatives (*8*). Xanthone-containing fractions, free of hypericin and tannins, of a hydroalcoholic extract of *H. perforatum* showed significant inhibition in vitro of MAO type A (which is specific for serotonin) (*57*). In other investigations, only the flavone aglycone, quercitrin, and the xanthone derivative, norethyriol, showed significant inhibition of MAO type A (*57–59*). Hypericin was excluded as the active constituent, and the flavonols and 1,3,6,7-tetrahydroxyxanthone were reported to be the active constituents of a crude extract of the herb (*57–59*). Molecular modelling studies of the constituents of the herb also indicated that the flavonoids may be the most likely candidates for inhibitors of MAO, as their structures are similar to those of known MAO type A inhibitors, toloxotone and brofaromine (*60*).

The MAO-inhibiting activity of six fractions of a hydroalcoholic extract of the herb was determined in vitro and ex vivo. In vitro inhibition of MAO type A in rat brain homogenates could only be shown at a concentration of 1–10 mmol/l of a crude extract or a flavonoid-rich fraction. In ex vivo studies using albino rats, neither the crude extract nor the xanthone-containing fractions inhibited MAO type A or MAO type B after intraperitoneal administration of 300 mg/kg body weight of the extract or 1–10 nmol/l of the fractions. In addition, purified hypericin did not inhibit MAO type A either in vitro or ex vivo (*61*).

The in vitro effects of hypericin, an ethanol extract, and fractions of the extract were tested for inhibition of MAO and COMT obtained from pig liver. Inhibition of MAO was seen with hypericin (1 mmol/l),[1] ethanol extract (0.1 mmol/l),[1] and a fraction containing hypericins and flavonols (0.01 mmol/l).[1]

[1] Molar concentrations were based on a mean molar mass of 500 (*62*).

Weak inhibition of COMT was observed with hypericin and the ethanol extract (both at a concentration of 1 mmol/l),[1] whereas two fractions, containing flavonols and xanthones, inhibited COMT to a greater extent at 0.1 mmol/l[1] (*62*). However, the inhibitory concentrations observed during this study appear to be too high to be of any clinical significance.

Other possible mechanisms of the antidepressant effect of Herba Hyperici include its ability to modulate the production of mediators of inflammation such as cytokines, particularly interleukins. Strong suppression of interleukin-6 (IL-6) release was observed in blood samples from depressed patients treated with *H. perforatum* extract (*63*). IL-6 is involved in the modulation of the hypothalamic–pituitary–adrenal (HPA) axis within the nervous/immune system. Elevated IL-6 levels activate the HPA axis, thus increasing levels of adrenal hormones that play a role in depression.

Effect on smooth muscle contraction

A 95% ethanol extract or tincture of the herb (200 µg/ml) inhibited barium- and histamine-induced smooth muscle contractions of guinea-pig ileum in vitro (*64*), and contractions of cat and mouse intestine (*65*). An ethyl acetate extract of the herb (0.1 mg/ml) inhibited potassium chloride- and histamine-induced contractions in pig coronary artery in vitro (*66*).

Antibacterial and antiviral activity

A methanol extract of Herba Hyperici inhibited the growth in vitro of *Escherichia coli*, *Proteus vulgaris*, *Streptococcus mutans*, *Streptococcus sanguis*, *Staphylococcus oxford* and *Staphylococcus aureus (*MIC 0.31–1.25 mg/ml) (*67*). An acetone, hot aqueous or ethyl acetate extract of the herb was active against influenza virus A2 (Mannheim 57), herpes simplex virus 2, poliovirus II and vaccinia virus in vitro (*68*, *69*). However, a decoction or hydroalcoholic extract of *H. perforatum* dried stem was not active against herpes simplex virus 1 or 2, or HIV in vitro (100 µg/ml) (*70*). In vitro activity of hypericin has been demonstrated against Friend murine leukaemia virus, hepatitis B virus, murine cytomegalovirus, human cytomegalovirus (Davis strain), parainfluenza 3 virus, Sindbis virus, vaccinia virus, vesicular stomatitis virus and equine infectious anaemia virus (*71–77*). Hypericin and pseudohypericin also inhibited herpes simplex virus types 1 and 2, and HIV-1 in vitro (*75*, *77–83*). Hypericin inhibited the activity of HIV reverse transcriptase in vitro (IC_{50} 0.77 mmol/l) (*74*, *80*, *84*), and inhibited herpes simplex virus, Rauscher murine leukaemia and Friend murine leukaemia viruses in mice after intravenous, intraperitoneal or intragastric administration (*80–82*). Intraperitoneal administration of a 5% aqueous extract of the herb to mice resulted in viricidal activity against tick-borne encephalitis virus (*85*). Hypericin displayed marginal activity in vitro against Molony murine leukaemia virus and did not show selective activity against herpes simplex

[1] Molar concentrations were based on a mean molar mass of 500 (*62*).

virus, influenza virus A, adenovirus or poliovirus (*82*). However, incubation of the virus with hypericin prior to infection resulted in viricidal activity against all enveloped viruses tested (IC_{50} 1.56–25 μg/ml), but not against non-enveloped viruses (*82*). The antiviral activity of hypericin appears to involve a photoactivation process that forms a singlet oxygen and inactivates both viral fusion and syncytia formation (*72*, *75*, *86*).

Protein kinase C inhibition

Numerous in vitro studies have demonstrated that hypericin is a potent inhibitor of protein kinase C (*87–92*). Hypericin treatment of glioma cell lines inhibited growth and also induced cell death due to protein kinase C (*93*). Receptor tyrosine kinase activity of epidermal growth factor is also inhibited by hypericin and may be linked to its antiviral and antineoplastic effects (*89*, *94*). The inhibition of protein kinase C may contribute to the anti-inflammatory effects of Herba Hyperici, as hypericin also inhibited the release of arachidonic acid and leukotriene B4 (*94*).

Wound healing

External application of a 20% aqueous extract of the crude drug to the skin of guinea-pigs and rabbits accelerated healing of experimentally induced wounds (*95*, *96*). Intragastric administration of a 60% ethanol extract of the dried leaves to rats (0.1 ml/animal) accelerated healing of experimentally induced wounds by enhancing the strength and rate of wound contraction and epithelialization (*97*).

Clinical pharmacology

Antidepressant activity

Clinical trials without controls

The safety and efficacy of oral administration of Herba Hyperici has been assessed in more than 5000 patients in numerous case reports and studies (*22*, *23*, *31*, *98*). In a drug-monitoring study involving 3250 patients, 49% were assessed as being mildly depressed, 46% as moderately depressed and 3% as severely depressed at the beginning of the trial. The patients were treated with 300 mg of a dried 80% methanol extract of the herb three times daily, and evaluated after 2 and 4 weeks of therapy. After treatment, 80% of patients had improved or were symptom-free, while 13–16% remained unchanged or were worse. Minor adverse reactions were reported in 2.4% of patients (*31*). A post-marketing trial was performed with 2404 patients with symptoms of mild to moderate depression who were treated with 2–4 capsules of an ethanol extract of the herb (equivalent to 0.6–1.8 mg total hypericin) daily for 4–6 weeks. Symptomatic improvement was evaluated as good to very good in 77% of patients and satisfactory in 15% (*99*).

The effects of an ethanol extract of the herb on the electroencephalogram (EEG) of 40 patients with depression were determined following administra-

tion of the extract (equivalent to 0.5 mg total hypericin or 1.4 g crude drug) daily for 4 weeks. An increase in theta-activity, a decrease in alpha-activity and no change in beta-activity were observed, indicating the induction of relaxation (*100*). A significant increase in nocturnal melatonin plasma concentration was observed in 13 healthy subjects treated with a hydroethanolic extract of the herb (equivalent to 0.53 mg total hypericin) daily for 3 weeks (*101*). A significant increase in the concentration of neurotransmitters in the urine was observed 2 hours after administration of a standardized ethanol extract of the crude drug to six women with symptoms of depression (*42*).

Reviews of clinical trials

The results from over 28 controlled clinical trials involving oral administration of Herba Hyperici have been published. Twelve of the trials, involving 950 patients, were conducted using an ethanol extract of the herb, while the other 16 trials of 1170 patients used a dried 80% methanol extract (*26*). A systematic review and meta-analysis of 23 of the randomized clinical trials involving 1757 patients assessed the efficacy of the herb in the symptomatic treatment of mild to moderate depression. Twenty trials were double-blind, one was single-blind and two were open studies. Fifteen of the trials involving 1008 patients were placebo-controlled and eight studies of 749 patients were comparison trials with other antidepressant drugs. With the exception of two trials, all studies had treatment periods of 4–8 weeks. The daily dosage ranged from 0.4 to 2.7 mg hypericin in 300–1000 mg of a standardized extract of the herb. Seventeen trials used the Hamilton Rating Scale for Depression (Hamilton Depression Rating Scale), which focuses primarily on somatic symptoms, to measure effectiveness, while 12 trials used the Clinical Global Impression Scale. The latter involves observer-rated analysis of severity of illness, global improvement and efficacy. The meta-analysis concluded that the herb was significantly superior to the placebo and was as effective as standard antidepressants such as maprotiline or imipramine (75 mg three times daily). Fewer side-effects were seen in the herb-treated patients (19.8%) than in those receiving standard antidepressants (52.8%) (*21*).

A systematic, criteria-based review of 18 controlled clinical trials using either ethanol or methanol extracts of the herb as a treatment for depression was carried out. Twelve of the trials (nine placebo-controlled and three comparison trials) met the methodological inclusion criteria and were included in the review. The results of the cumulative data show that extracts of the herb were superior to the placebo for the symptomatic treatment of depression as measured by the Hamilton Depression Rating Scale. Results of the comparison studies with maprotiline (75 mg daily) and imipramine (50–75 mg daily) and other standard antidepressants suggest that extracts of the herb have a similar therapeutic profile. Some flaws in the reported studies included no intention to treat analysis, lack of control over compliance, and insufficient description of the extract or placebo used (*19*).

A review of 12 double-blind, placebo-controlled and three comparison clinical trials assessed the efficacy of the herb for the treatment of mild to moderate depression, and the methodology used to perform the studies. The review concluded that the antidepressant activity of a standardized extract of the herb (300 mg standardized to contain 0.9 mg hypericin three times daily for 4–8 weeks) was sufficiently documented. However, it also concluded that no dose-finding studies had been conducted, and that studies on inpatients with severe depression and endogenously depressed patients were lacking. In the three comparison studies, the daily dose of 75 mg maprotiline or 30 mg amitriptyline was viewed as too low. The review concluded that further trials of longer duration in comparison with higher doses of standard antidepressants are warranted (*27*).

A double-blind, randomized, multicentre study was performed to evaluate the efficacy, safety and tolerability of a daily dose of 900 mg hydroalcoholic extract of the herb or 75 mg amitriptyline. After a 1-week placebo run-in phase, 156 patients were treated with 300 mg extract or 25 mg amitriptyline, three times daily for 6 weeks. The patients were assessed before and after treatment. The Hamilton Depression Rating Scale changed from 20 to 10 in the extract-treated patients and from 21 to 6 in the amitriptyline-treated patients ($P < 0.05$). The Montgomery-Asberg Rating Scale for Depression changed from 27 to 13 in the extract-treated patients, and from 26 to 6.5 in the amitriptyline-treated patients ($P < 0.05$). Similar scores in the Clinical Global Impression Scale were observed in both groups (*29*). In a randomized, double-blind, multicentre trial the effectiveness of a standardized dried 80% methanol extract of the herb (containing 0.3% hypericin) was compared with that of imipramine in 209 patients with recurrent depressive disorder, current episode severe without psychotic symptoms (*18*). Patients were treated daily with 1800 mg extract or 150 mg imipramine for 6 weeks. Assessment of patients before and after treatment revealed the following changes. In the Hamilton Depression Rating Scale: from 25.3 to 14.4 in the extract-treated patients, and from 26.1 to 13.4 in the imipramine-treated patients ($P < 0.021$). In the von Zerssen Depression Scale: from 28.9 to 13.6 in the extract-treated patients, and from 26 to 6.5 in the imipramine-treated patients ($P < 0.05$). Results in the Clinical Global Impression Scale showed a trend in favour of imipramine. Although the efficacy of the extract was not significantly different from that of imipramine, analysis of the patient subgroups showed that it was most effective in patients with moderately severe depression (*28*).

A prospective, randomized, double-blind, placebo-controlled, multicentre study assessed the safety and efficacy of a standardized ethanol extract of the herb for the treatment of 151 patients with mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in 1CD-10 (*18*)). Patients received either one 250 mg tablet of the extract (equivalent to 1 mg hypericin) or a placebo twice daily for 6 weeks. The primary efficacy variable was the Hamilton Depression Rating Scale, and secondary variables were the risk–benefit Clinical Global Impression Scales I–III and Visual Analogue Scale

(a validated, patient self-assessment test). Decreases were seen in the Hamilton Depression Rating Scale in 56% of patients treated with the extract, whereas decreases were seen in only 15% of patients who received the placebo (*24*). A randomized, double-blind, placebo-controlled, multicentre study assessed the clinical efficacy and safety of two extracts of the herb differing in their hyperforin content (0.5% or 5.0% hyperforin) in 147 patients suffering from mild to moderate depression as classified in the *Diagnostic and statistical manual of mental disorders*, 4th ed. (DSM-IV) of the American Psychiatric Association (*102*). The patients received either 900 mg of one of the extracts or a placebo daily for 42 days. The patients who received the extract containing 5% hyperforin showed the largest decrease in the Hamilton Depression Rating Scale (a reduction of 10.3; $P = 0.004$, compared to the placebo). A reduction of 8.5 following treatment with the extract containing 0.5% hyperforin and of 7.9 in the placebo-treated group was seen (*20*).

In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers treated with a dried hydromethanolic extract of the herb (300 mg three times daily for 4 weeks) showed improved sleep quality with an increase in deep-sleep phases (*25*). A randomized, double-blind, placebo-controlled study of 54 healthy volunteers evaluated the central pharmacodynamic effects of two extracts of the herb with different hyperforin contents (0.5% or 5.0%) but identical hypericin content. Healthy volunteers received either 900 mg (300 mg three times daily) of one of the extracts or a placebo daily for 8 days. A quantitative topographic electroencephalogram (qEEG) was performed on days 1 and 8 as an indicator of drug-induced pharmacological activity. In both treatment groups, reproducible central pharmacodynamic effects were observed between 4 and 8 hours after administration, and were confirmed on day 8. The extract containing 5% hyperforin showed a marked tendency to produce greater increases in qEEG baseline power performances than the extract containing 0.5% hyperforin. Higher baseline outputs were observed on day 8 in the delta-, theta- and alpha-1 frequencies. Patients treated with the extract containing 5% hyperforin had an increase in qEEG power performance in the delta-frequency after a single dose and in the theta- and alpha-1 frequencies after 8 days of treatment, when compared with placebo treatment (*103*).

In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers were treated with 900 mg (300 mg three times daily) of a dried hydromethanolic extract of the herb for 6 weeks, and the effects on the EEG were assessed. A reduction in alpha-activity and audiovisual latencies in evoked potentials and an increase in beta- and theta-activities were demonstrated (*104*). Another randomized, double-blind, clinical trial of 24 healthy volunteers compared the effects of a dried hydromethanolic extract of the herb with those of maprotiline on the resting EEG and audio-visual latencies in evoked potentials. After 4 weeks of treatment, an increase in theta- and beta-2 activity was observed in patients treated with 900 mg of a standardized hydroalcoholic extract (300 mg three times daily), while a decrease in theta-activity was seen in patients treated with 30 mg maprotiline (10 mg three times

daily) (*105*). The extract also induced an increase of deep sleep as demonstrated by visual analysis of the sleeping phases and automatic analysis of slow-wave EEG activities. Rapid eye movement sleep was not influenced (*25*).

A randomized, single-blind study evaluated the efficacy of the herb for the treatment of seasonal affective disorders (SAD) in conjunction with light therapy. Twenty patients with SAD were treated with 900 mg (300 mg three times daily) of a hydroalcoholic extract of the herb daily for 4 weeks, combined with either bright (3000 lux) or dim light (<300 lux) conditions. Light therapy was carried out for 2 hours daily. A significant reduction of the Hamilton Depression Rating Scale in both groups, but no statistically significant difference between the two groups, was observed (*106, 107*).

Photodynamic effects

The photodynamic effects of hypericin, incorporated into a non-ionic hydrophilic ointment base, were assessed after external application to the skin of patients with herpes communis. The infected dermal surface of treated patients recovered rapidly and the effects lasted in most cases (*33*).

Pharmacokinetics

Single-dose pharmacokinetics of hypericin and pseudohypericin were determined in 12 healthy male volunteers. After a single dose of 300, 900 or 1800 mg extract (equivalent to 250, 750 or 1500 µg hypericin, respectively, and 526, 1578 or 3156 µg pseudohypericin, respectively), plasma levels of the hypericins were measured by high-performance liquid chromatography for up to 3 days. The median plasma levels were 1.5, 4.1 and 14.2 ng/ml for hypericin, and 2.7, 11.7 and 30.6 ng/ml for pseudohypericin, for the three stated doses, respectively. The median half-life of hypericin was 24.8–26.5 hours and 16.3–36.0 hours for pseudohypericin. The median lag-time of absorption was 2.0–2.6 hours for hypericin and 0.3–1.1 hours for pseudohypericin. During long-term dosing (900 mg daily), a steady state was reached after 4 days. The mean maximum plasma level during the steady state was 8.5 ng/ml for hypericin and 5.8 ng/ml for pseudohypericin (*108*).

A randomized, placebo-controlled clinical trial was performed to evaluate the pharmacokinetics and dermal photosensitivity of hypericin and pseudohypericin in 13 healthy volunteers after administration of a single dose of either a placebo or 900, 1800 or 3600 mg of the extract (equivalent to 0.00, 2.81, 5.62 and 11.25 mg total hypericin [combined hypericin and pseudohypericin], respectively). The maximum total hypericin plasma levels observed at 4 hours after administration were 0, 28, 61 and 159 ng/l, respectively. Before and 4 hours after drug intake, the subjects were exposed to increasing doses of solar-simulated irradiation on small areas of their backs. No dose-related increase in light sensitivity was observed. In the multiple-dose analysis, 50 healthy volunteers received 600 mg extract of the herb three times during 1 day only. A slight increase in solar-simulated irradiation sensitivity was observed (*109*).

In a randomized, four-way crossover study without controls involving six healthy volunteers, the pharmacokinetics of hyperforin were determined after administration of single doses of 300, 600, 900 or 1200 mg of an alcohol extract containing 5% hyperforin. The maximum plasma level of hyperforin (150 ng/ml) was reached 3.5 hours after administration of 300 mg of the extract. The hyperforin half-life and mean residence time were 9 and 12 hours, respectively. The pharmacokinetics were linear up to 600 mg of the extract. Increasing the dose to 900 or 1200 mg of extract resulted in values for maximum clearance and area under the curve lower than those expected from linear extrapolation of data from the lower doses (*110*). The pharmacokinetics of hyperforin were studied in nine healthy volunteers, as part of a double-blind, randomized, placebo-controlled study of 54 subjects. The subjects received either a single dose of 900 mg of an alcohol extract containing 5% hyperforin, or 300 mg of an alcohol extract containing 5% hyperforin three times daily for 8 days. No accumulation of hyperforin in the plasma was observed. On the basis of the area under the curve values from the multiple-dose study, the estimated steady-state plasma concentration of hyperforin was approximately 100 ng/ml (*110*).

Contraindications

Herba Hyperici is contraindicated in cases of known allergy to plants of the Clusiaceae family.

Warnings

As with other antidepressant drugs, observation of the therapeutic effects of Herba Hyperici may require 2–4 weeks of therapy. If a significant antidepressant effect is not observed after 6 weeks of treatment, a physician should be consulted.

Precautions

General

Ultraviolet treatments or prolonged exposure to direct sunlight should be avoided when Herba Hyperici is used, as photosensitization may occur in light-sensitive individuals (*32*). (See Adverse reactions.)

Drug interactions

Although the ingestion of foods containing high concentrations of tyramine such as pickled or smoked foods and cheese, and selective serotonin reuptake inhibitors such as fluoxetine are contraindicated with MAO inhibitors, in vivo data linking Herba Hyperici to MAO inhibition are lacking (*111*, *112*). The com-

bination of Herba Hyperici with other standard antidepressant drugs, such as tricyclic antidepressants or fluoxetine, is not recommended, unless under medical supervision.

There are now numerous reports in the medical literature indicating that Herba Hyperici extracts induce hepatic enzymes that are responsible for drug metabolism and may reduce the serum levels and therapeutic efficacy of drugs (*113–117*). Coadministration of theophylline with a Herba Hyperici extract lowered the serum level of theophylline in a patient previously stabilized, requiring an increase in the theophylline dose (*113*). Coadministration of Herba Hyperici and digoxin reduced serum digoxin concentrations after 10 days of treatment (*114*). A decrease in serum cyclosporin, warfarin and phenprocoumon concentrations was seen in patients after they had additionally taken Herba Hyperici extracts (*115*). Concomitant use of Herba Hyperici in five patients previously stabilized on serotonin-reuptake inhibitors resulted in symptoms of central serotonin excess (*116*). The United States Food and Drug Administration has publicized a report concerning a significant drug interaction between Herba Hyperici and indinavir, a protease inhibitor used to treat HIV infections (*117*). Herba Hyperici substantially reduced indinavir plasma concentrations, due to induction of the cytochrome P450 metabolic pathway. As a consequence, the concomitant use of Herba Hyperici and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is not recommended and may result in suboptimal antiretroviral drug concentrations, leading to a loss of virucidal activity and the development of resistance (*117*).

Carcinogenesis, mutagenesis, impairment of fertility

The mutagenicity of hydroalcoholic extracts of Herba Hyperici containing 0.2–0.3% hypericin and 0.35 mg/g quercetin has been studied in various in vitro and in vivo systems (*118–121*). The in vitro studies were performed using the *Salmonella*/microsome assay, hypoxanthine guanidine phosphoribosyl transferase test (up to 4 µl/ml), unscheduled DNA synthesis test (up to 1.37 µl/ml), cell transformation test in Syrian hamster embryo cells (up to 10 µl/ml) and spot test in mice (up to 10 µl/ml). The in vivo tests included the chromosome aberration test with bone marrow cells of Chinese hamsters (10 ml/kg body weight, gastric lavage) and the micronucleus test in rodent bone marrow (2 g/kg body weight, gastric lavage). Although some positive results were observed in vitro in the *Salmonella*/microsome assay (*119*, *121*), all the in vivo tests were negative, indicating that the hydroalcoholic extract was not mutagenic in animals. In a 26-week study, intragastric administration of the hydroalcoholic extract to rats and dogs (900 and 2700 mg/kg body weight) had no effect on fertility, development of the embryo, or pre- or postnatal development (*122*).

Other precautions

No information available on precautions concerning drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing

mothers; or paediatric use. Therefore, Herba Hyperici should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions

Phototoxicity has been reported in cattle after ingestion of *H. perforatum* during grazing. However, the doses were estimated to be approximately 30–50 times higher than normal therapeutic doses (*123*). Photosensitization in light-sensitive individuals has been demonstrated in a controlled clinical trial involving metered doses of hypericin and exposure to ultraviolet A and B irradiation. Patients were treated with 600 mg of a hydroalcoholic extract of the herb (containing 0.24–0.32% total hypericin) three times daily for 15 days. A measurable increase in erythema in light-sensitive individuals was observed after ultraviolet A irradiation. The plasma concentration of hypericin and pseudohypericin in these subjects was double that seen during normal therapeutic treatment of depression (*124*). A single case of reversible erythema after exposure to ultraviolet B has been reported in one patient who had been taking the herb for 3 years (*125*). A single case of acute neuropathy after exposure to sunlight has been reported in one patient taking the herb (*126*). Drug-monitoring studies indicate that side-effects of the herb are rare and mild, and include minor gastrointestinal irritations, allergic reactions, tiredness and restlessness. However, these studies did not last longer than 8 weeks (*21*, *24*, *31*). Clinical studies have suggested that the use of the herb does not affect general performance or the ability to drive (*127*, *128*).

Dosage forms

Dried crude drug for decoction, powdered drug or extracts in capsules, tablets, tinctures and drops (*2*, *7*, *32*). Topical preparations include the oil, infusions, compresses, gels and ointments. Store in a well-closed container, protected from light (*10*, *11*).

Posology

(Unless otherwise indicated)

Daily dosage: 2–4 g crude drug (*32*). Internal use: standardized tinctures or fluidextracts (*23*, *98*, *100*), or standardized hydroethanolic or dried hydromethanolic extracts, up to a daily dose of 900 mg extract (equivalent to 0.2–2.7 mg total hypericin) (*19*, *21*, *22*, *27*, *31*).

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