Summary
Kurt Hostettmann and Jean-Luc Wolfender
Phytochemistry

Hypericum perforatum, as well as other members of the Hypericaceae, is a prolific producer of secondary metabolites and has been the subject of numerous phytochemical investigations due to its ancient use as a vulnerary and especially, more recently, its widespread application as a potent antidepressant phytopreparation. Numerous constituents including naphtho-dianthrones, phloroglucinols, flavonoids, biflavonoids, xanthones, proanthocyanidins, acid phenols as well as essential oils have been described in this plant. The most characteristic is certainly hypericin, a red pigment endowed with many interesting biological activities. More recently the phloroglucinol derivatives, and particularly hyperforin, have been the centre of various studies because of its possible key role in the antidepressant activity of the extract. Today, the standardisation of the extract resides mainly on the complete profiling of all biologically active constituents, since the biological effects of *H. perforatum* are now mainly considered to be from the presence of a single constituent, rather than from the whole mixture of the metabolites.

Summary
Marco Gobbi and Tiziana Mennini
St. John's Wort and its active principles in depression and anxiety – A critical analysis of receptor binding studies

In vitro receptor binding assays have measured the affinities of many constituents of St. John's Wort (SJW) extracts for almost all the central neurotransmitter receptors, to gain information on the mechanism(s) of action and on the active principle(s) underlying its antidepressant/anxiolytic properties.
The main conclusion from *in vitro* binding data is that the central effects of SJW extracts are not due to hypericin or hyperforin interacting directly with most of the central neurotransmitter transporters and receptors, because the concentrations required for these interactions (> 500 nM) far exceed those found in the brain after pharmacologically effective doses of the extract (< 50 nM). The only possible exceptions are the relatively high affinities reported for hypericin on DA3 or CRF-1 receptors (34 and 300 nM, respectively). Amentoflavone also interacts with high affinity to benzodiazepine receptors (6–15 nM) but unfortunately this finding cannot be adequately interpreted because of the lack of pharmacokinetic data on the brain levels of this important constituent after treatment with SJW extracts.

Key Words: Hypericum perforatum L., St. John's Wort, hyperforin, hypericin, amentoflavone, depression, anxiety, neurotransmitter receptors, monoamine transporters, in vitro binding assays.

Summary
Kristina Treiber and Walter E. Müller
Effects on transmitter uptake and their cellular and molecular basis

St. John's Wort extract inhibits the neuronal uptake of serotonin, norepinephrine, and dopamine, in this regard resembling to most old and new synthetic antidepressant drugs. However, in contrast to other antidepressants it also inhibits uptake of gamma-aminobutyric acid (GABA) and L-glutamate. No other antidepressant shows a similar broad inhibitory profile. Out of the many known different constituents of St. John's Wort, only hyperforin and its structural analogue adhyperforin are responsible for this effect. Interestingly, unlike

classical antidepressants both hyperforin and adhyperforin do not act as competitive inhibitors at the transmitter binding sites of the transporter proteins. Although the detailed molecular mechanism of uptake inhibition is still under investigation, most evidence points to an elevation of intracellular sodium concentration as primary mechanism which in turn leads to an inhibition of sodium dependent neurotransmitter transporters. The increase of intracellular sodium and additionally of intracellular calcium can be explained by the activation of non-selective cation channels (NSCCs) or transient receptor potential channels (TRP channels), possibly associated with alterations of membrane fluidity. Additionally, hyperforin inhibits vesicular uptake of monoamines and also enhances release of monoamines from vesicles. Thus, Hyperforin has a broad spectrum of pharmacological activities that is mildly affecting many neurotransmitter systems. This might explain the additional pharmacological effects of St. John's Wort extract beyond those of typical antidepressant drugs.

Key Words: ^{3}H-CGP 12177, ^{3}H-CGP 12177 binding, ^{3}H-citalopram binding, ^{3}H-paroxetine binding, adhyperforin, armentoflavone, biapigenin, catechine, citalopram, clomipramine, desipramine, dopamine, flavonoid, flufenamic acid, fluoxetine, fuvoxamine, GABA, Gadolinium, GTPase activity, hyperforin, hypericin, hypericin/pseudohypericin, hyperoside, imipramine, intracellular sodium concentration $[Na^{+}]_{i}$, isoquercitrin, kaempferol, Lanthan, L-Glutamate, LOE 908, MAO inhibition, membrane fluidity, monoamine transporter, myricetin, Na^{+}/Ca^{+} exchanger, Na^{+}/Cl-dependent transporter, Na^{+}/H^{+} exchanger, Na^{+}-K^{+} ATPase, non-selective cation channel (NSCCs), norepinephrine, oligomeric procyanidin fraction, polyphenol, protonophore FCCP, quercitrin, rutin, serotonin, sertaline, SK&F 96365, sodium ionophore monensin, synaptosomal uptake, TRP channel, vesicular membrane, vesicular uptake, voltage-dependent sodium channel, β receptor density, β-downregulation.

Summary

Jan Kehr, Sven Ove Ögren and Takashi Yoshitake

Modulation of neurotransmitter release and metabolism

This Chapter reviews the effects and the mechanisms of action of St. John's Wort (*Hypericum perforatum*) extracts on the release and metabolism of serotonin, noradrenaline and dopamine in the rat brain compared with synthetic antidepressants. The review is based on the results obtained with neurochemical techniques such as *ex vivo* tissue analysis and *in vivo* microdialysis. Most of the *in vitro* and *in vivo* results indicate that the noradrenergic system is only minimally affected by *Hypericum*. Microdialysis and electrophysiological studies suggest that the action of *Hypericum* extracts or its constituent hyperforin on 5-HT functions *in vivo* is relatively weak and differs from that of the conventional selective serotonins (SSRIs). Recent results obtained by microdialysis show that *Hypericum* extracts markedly increase the extracellular levels of dopamine in the prefrontal cortex and hippocampus. This suggests that the antidepressant effect of St. John's Wort may be associated with its stimulatory effects on mesolimbic and mesocortical dopamine pathways involved in control of motivation and reward.

Key Words: *Hypericum perforatum*, hyperforin, catecholamines, 5-HT, NA, DA, acetylcholine, glutamate, GABA, neurotransmitter release, microdialysis, depression, mood disorders, antidepressants.

Summary
Carla Gambaran and Daniela Giachetti
Efficacy in behavioural models of antidepressant activity

Extracts of *Hypericum perforatum* have been tested in experimental models of depression in rodents and their efficacy in these models has been demonstrated after acute, subacute, or repeated administration. In order to identify the component responsible for this activity, extracts with different proportions of hyperforin, currently the most likely active antidepressant principle, have been tested. Different groups reported a correlation between efficacy in these models and the hyperforin content of the extract. Moreover, purified hyperforin is active at doses significantly lower than those necessary for observing an activity when the extract is used. In conclusion, we now have convincing experimental evidence of the efficacy of *Hypericum perforatum* extract in models of depression.

Key Words: Escape deficit, forced swimming test, hyperforin, hypericin, *Hypericum perforatum*, *Hypericum perforatum angustifolium*, mouse, rat, stress, tail suspension test.

Summary
Michael Nöldner
Comparative preclinical antidepressant activity of isolated constituents

Extracts of the medicinal plant *Hypericum perforatum* L. (St. John's Wort) are widely used for the treatment of depressive diseases. Many of the plant constituents have been identified and some show biological activities which could contribute to the antidepressant effects of the plant extract. The phloroglucinol derivative hyperforin appears to be one of the most important constituents of *Hypericum* extracts, because it is a broad neurotransmitter reuptake inhibitor showing a pharmacological profile that could at least partially explain the antidepressant properties of the extracts. Besides hyperforin, some flavonols and biflavones have antidepressant-like activities in animal models of depression. Hypericin, which is responsible for the phototoxic effects of *Hypericum*, may be involved in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis, which is disturbed in depressed patients. It therefore appears that different constituents of *Hypericum perforatum* may contribute to the antidepressant activity of the total extract. Although much research has been done to identify and characterise the active constituents in the extract, there are still many questions about their efficacy and modes of action.

Key Words: Hypericum extract, hyperforin, flavonols, hypericin, rutin, antidepressant, pharmacology.

Summary
Shyam S. Chatterjee
Hyperforin and efficacy in animal models for anxiety and cognition

Until recently, most clinical and preclinical studies with extracts and secondary metabolites of St. John's Wort have concentrated on their antidepressant-like therapeutic potentials only. More recent findings indicate that extracts of the herb could be of interest for therapies of other comorbid mental health conditions like anxiety or cognitive disturbances. These additional therapeutic potentials of the herb became apparent only after hyperforin was identified as quantitatively the major neuroactive secondary metabolite of the herb. This Chapter summarises available information on anxiolytic and cognitive function improving

activities of St John's Wort extracts in animal models, and points out possible roles of hyperforin in these effects of the extracts. Some therapeutic and other implications of these more recent findings will be discussed also.

Key Words: St. John's Wort extracts, hyperforin, depression, anxiety, learning and memory, co-morbidity, therapy, behavioural models, cholinergic neurotransmission.

Summary
Mario Wurglics and Manfred Schubert-Zsilavecz
Pharmacokinetics and biopharmaceutics

Pharmacokinetic profile of hyperforin, hypericins and flavonoids

Hypericum perforatum (St. John's Wort, SJW) counted among the favorite herbal drugs and is the only herbal alternative to classical synthetic antidepressants in the therapy of mild to moderate depression. Several clinical studies have been conducted to verify the effectiveness of ethanolic or methanolic extracts.
Alcoholic SJW-extracts are a mixture of substances with a widly varying physical and chemical properties and activities. Hyperforin, a phloroglucinol-derivative, is the main source of pharmacological effects caused by the consumption of alcoholic extracts of St. John's Wort in the therapy of depression. However, several studies indicate that flavone-derivatives, e.g. rutin and also the naphthodianthrones hypericin and pseudohypericin, take part in the antidepressant efficacy.
In contrast to the good documentation concerning clinical efficacy, the oral bioavailability and the pharmacokinetic data about the active components is rather poor.
The hyperforin plasma concentration in humans was investigated in a small number of studies. The results of these studies indicate a relevant plasma concentration, comparable to that used in *in vitro* tests. Furthermore hyperforin is the only ingredient of *Hypericum perforatum* that could be determined in the brain of rodents after oral administration of alcoholic extracts.
The plasma concentrations of the hypericins were, compared to hyperforin, only a tenth, and until now the hypericins could not be found in the brain after oral administration of alcoholic *Hypericum* extracts or pure hypericin.
Until now, neither the pharmacokinetic profile nor the bioavailability of the flavonoids have been investigated after oral administration of an alcoholic *Hypericum* extract in humans or animals. Data is only available for rutin and the aglycone quercetin after administration of pure substances or other flavonoid sources.

Biopharmaceutical characterisation of SJW-products

In general, the biopharmaceutical quality and behaviour of herbal medicinal products (HMPs) is not well documented. Moreover, the regulatory situation in the developed countries with respect to quality control of HMP`s various considerably.
Quality parameters, including confirmation of label strength, content uniformity and release properties, of SJW-preparations are rare.
Published data of in vitro dissolution showed significant differences between the constituents. While the hydrophilic flavonoids dissolved well in all tested media, for hyperforin and hypericin surfactants, like bile constituents, are necessary.
The results of the dissolution variuos media show that there are also glaring differences in the release properties of various products containing SJW extract.

Summary
Siegfried Kasper
Clinical efficacy in depression

(no summary and keywords available)

Summary
Hans-Peter Volz
Clincal efficacy of St. John`s Wort in psychiatric disorders other than depression

There is some evidence that St. John`s Wort extracts might also work in other indications than depression. The most compelling evidence exists for efficacy in somatoform disorder. Two well-performed positive placebo-controlled trials have been pubished (Volz et al., 2002; Müller et al., 2004), demonstrating good efficacy of LI 160, a standardized hypericum extract, in a dose of 600 mg/day.
There is some evidence for efficacy of St. John`s Wort in premenstrual syndrome, in menopausal symptoms, in fatigue syndrome, obsessive-compulsive disorder and generalized anxiety disorder, however, placebo-controlled trials in these indications still have to be performed.

Summary
Volker Schulz and Andreas Johne
Side effects and drug interactions

Observational studies with preparations of St. John's wort have recorded an incidence of adverse events among patients of between 1% and 3%. This is some 10 times less than with synthetic antidepressants. The most common adverse events (1 per 300,000 treated cases) among the spontaneous reports in the official register concern reactions of the skin exposed to light. Investigations in volunteers have shown that the threshold dose for an increased risk of photosensitisation is about 2–4 g/day of a usual commercial extract (equivalent to approximately 5–10 mg of the hypericin that causes the phenomenon). The possibility of photosensitivity reactions should also be taken into account when therapy is combined with drugs that are known to increase photosensitivity. In view of further side effects and interactions, additional restrictions on use appear justified: as with all preparations in this group of indications, *Hypericum* preparations must not be taken concurrently with other antidepressants. If co-medication with coumarin-type anticoagulants is unavoidable, physicians are advised to closely monitor clotting parameters. Co-medication with cyclosporin and indinavir, and other protease inhibitors used in anti-HIV treatment, is contraindicated. The possibility of an interaction with oral contraceptives needs further research.

Key Words: St. John's Wort extract, side effects, drug interactions.

Summary
Michael Franklin
Endocrinology of St. John's Wort extract

Overall, acute treatment studies with various extracts of HP suggest that its antidepressant effects are probably mediated in the main through alterations in 5-HT and DA neurotransmission and do

not generally involve NA. This is certainly the case in the time frame in which the studies reported here have been carried out in. With respect to DA-mediated processes, studies have demonstrated that HP extracts decrease plasma prolactin in both animals and man and that this is dose-dependent in the rat. It also increases GH in man. Of the active ingredients in HP extracts studied, hyperforin but not hypericin was shown to decrease plasma prolactin; biochemical, pharmacokinetic and clinical findings lend support to these findings. The HP extract LI 160, hyperforin and hypericin all increase serum corticosterone in the rat, which from blockade studies appeared to be mediated via a post-synaptic 5-HT_2 receptor mechanism. LI 160 also increased salivary cortisol in man. Some hormone responses to HP extract single dose and subchronic administration demonstrated nonlinear dose-response relationships and may possibly be U-shaped in nature.

Sub-chronic treatment studies in the rat showed reduced serum corticosterone and increased serum prolactin responses when compared to acute treatment with an HP extract at two different doses. Further, both serum corticosterone and prolactin responses to neuroendocrine challenge with the 5-HT_{2A} agonist DOI following treatment for 2 weeks with an extract of HP, were reduced compared to placebo. Thus post-synaptic 5-HT_2 receptors may downregulate or are desensitised with respect to corticosterone output and that DA inhibitory control of prolactin release may be reduced due to increases in 5-HT-mediated influences. CRF mRNA gene expression studies lend support to these findings. In a recent clinical trial carried out in healthy male volunteers, salivary cortisol response-profiles following 7 days treatment with two different doses of the extract LI 160 were increased, but this was greater at the lower dose. The authors suggested that HP may exhibit a nonlinear dose-response U-shaped relationship with respect to salivary cortisol output. In the same study the rise in evening salivary melatonin was not altered by either dose. It was suggested that since melatonin output is mostly NA driven, that treatment with HP, certainly in the shorter term, probably does not effect NA neurotransmission.

Further studies are required to confirm 5-HT and DA-mediated mechanisms of action of HP extracts utilising the neuroendocrine paradigm and to access more fully dose-response relationships. Studies have shown that hyperforin is probably the most important active ingredient of HP extracts. It is therefore perhaps important that clinical trials are performed in patients with mild-to-moderate depression to show that the efficacy of the HP extract under test is dependent on its hyperforin content, so that future HP treatments may be standardised on hyperforin content and not the present hypericin content.

Key Words: St John's Wort, Hypericum perforatum, hormone, prolactin, cortisol, growth hormone, 5-HT, dopamine, noradrenaline.

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