Hypericum Extract

Use in Depression
**EUROMED** HERBAL EXTRACTS SERIES 1. HYPERICUM

**Introduction**

**EUROMED** is a company specialized in botanical extracts and active principles which will be later used as phytomedicines within the pharmaceutical field. **EUROMED** devotes itself to the development and production of these therapeutically active raw materials.

For that purpose the botanical raw materials are subject to a strict selection and control, and the products are manufactured following production methods developed by the **EUROMED** company, which include controls in process in order to assure a standard quality according to the latest knowledge of the state of art in different fields: R&D, analysis, processes and facilities, therapeutical usages on a scientific basis.

**EUROMED** assures the quality of the products with the background of broad phytochemical know-how.
# HERBAL EXTRACTS SERIES 1. HYPERICUM

## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Hypericum Extract: General Information</td>
<td>4</td>
</tr>
<tr>
<td>1.1 Description</td>
<td>4</td>
</tr>
<tr>
<td>1.2 Indications</td>
<td>4</td>
</tr>
<tr>
<td>1.3 Extract Specification</td>
<td>4</td>
</tr>
<tr>
<td>1.4 Dosage and Methods of Administration</td>
<td>5</td>
</tr>
<tr>
<td>1.5 Contraindications and Interactions</td>
<td>5</td>
</tr>
<tr>
<td>1.6 Side-Effects</td>
<td>5</td>
</tr>
<tr>
<td>2  From Plant to Extract</td>
<td>7</td>
</tr>
<tr>
<td>2.1 St John’s Wort (Hypericum perforatum L.):</td>
<td></td>
</tr>
<tr>
<td>Botanical Information</td>
<td>7</td>
</tr>
<tr>
<td>2.2 Historic Use</td>
<td>9</td>
</tr>
<tr>
<td>2.3 Chemistry of the Plant Substances</td>
<td>10</td>
</tr>
<tr>
<td>2.4 Preparation of the Extract and Quality Assurance</td>
<td>11</td>
</tr>
<tr>
<td>2.5 Standardization</td>
<td>14</td>
</tr>
<tr>
<td>3  Depressive States</td>
<td>15</td>
</tr>
<tr>
<td>4  Pharmacology</td>
<td>19</td>
</tr>
<tr>
<td>4.1 Antidepressant Effect</td>
<td>19</td>
</tr>
<tr>
<td>4.1.1 Blocking the Resorption of Serontin</td>
<td>19</td>
</tr>
<tr>
<td>4.1.2 Slight Blocking of Monoamine oxidase (MAO)</td>
<td>21</td>
</tr>
<tr>
<td>4.1.3 Blocking of Catechol-O-methyltransferase (COMT)</td>
<td>22</td>
</tr>
<tr>
<td>4.1.4 Modulation of Cytokin Release</td>
<td>22</td>
</tr>
<tr>
<td>4.2 Pharmacokinetics</td>
<td>23</td>
</tr>
<tr>
<td>5  Toxicology</td>
<td>24</td>
</tr>
<tr>
<td>6  Clinical Pharmacology</td>
<td>25</td>
</tr>
<tr>
<td>6.1 Influence on Evoked Potentials and Resting EEG</td>
<td>25</td>
</tr>
<tr>
<td>7  Proof of Clinical Effectiveness</td>
<td>27</td>
</tr>
<tr>
<td>7.1 Meta-Analysis of the Clinical Trials of the use of</td>
<td>27</td>
</tr>
<tr>
<td>St John’s Wort Extract for Psychovegetative Complaints</td>
<td></td>
</tr>
<tr>
<td>7.2 Clinical Trials with Placebos</td>
<td>28</td>
</tr>
<tr>
<td>7.3 A Comparison of Clinical Trials and Standard Conditions</td>
<td>31</td>
</tr>
<tr>
<td>7.4 Drug-Monitoring Trials</td>
<td>33</td>
</tr>
<tr>
<td>7.5 Effect on Patients’ Responses</td>
<td>35</td>
</tr>
<tr>
<td>7.6 Therapeutic Safety</td>
<td>36</td>
</tr>
<tr>
<td>8  Bibliography</td>
<td>37</td>
</tr>
</tbody>
</table>
1 Hypericum Extract:
General Information

1.1 Description

Absolutely natural

Extract of *Hypericum* is a standardized herbal extract of St John’s Wort (*Hyperici herba*).

Herbal antidepressant

The herbal antidepressant *Hypericum* extract has a mood-enhancing and drive-improving effect as well as relieving both anxiety and tension. General capacity for enjoying life is increased.

Extract of *Hypericum* does not cause tiredness or affect responses. Because it does not interact with other drugs and is so well tolerated it is suitable for patients of all age groups as well as for patients with multiple diagnoses.

1.2 Indications

Indications for the therapeutic use of *Hypericum* extract are depressive states and psychovegetative disorders as well as anxiety and/or nervous agitation.

1.3 Extract Specifications

*Hypericum* extract is an extract of St John’s Wort containing between 0.1 - 0.3 % hypericin. St John’s Wort preparations usually contain circa 250 - 300 mg *Hypericum* extract (available from EUROMED).
1.4 Dosage and Methods of Administration

A daily oral dose of 500 - 900 mg *Hypericum* extract is usual. Usual length of therapy is 1 - 6 months. Discontinuation does not lead to side effects. Physicians monitoring is advised. Table 1 (page 6) provides an overview over the *Hypericum*-preparations of the market.

1.5 Contraindications and Interactions

None known.

1.6 Side-effects

*Hypericum* extract is generally well tolerated. In clinical trials rare cases of gastro-intestinal irritations occurred in the same percentage as in the placebo-group. In rare cases, especially in fair-skinned people, photosensitization can occur (increased sensitivity of the skin to sunlight).
Tab. 1: Preparations containing *Hypericum* extract with a standardized content of hypericin.

<table>
<thead>
<tr>
<th>Preparation Name</th>
<th>Method of Extraction</th>
<th>Content of Hypericin Extract [mg]</th>
<th>Total Extract/day [mg]</th>
<th>Content of Hypericin [mg]</th>
<th>Total Hypericin/Day [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jarsin 300</td>
<td>methanolic</td>
<td>300</td>
<td>900</td>
<td>0.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Remotiv</td>
<td>ethanolic</td>
<td>250</td>
<td>500</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Aristofort</td>
<td>ethanolic</td>
<td>120-180</td>
<td>480-720</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Divinol Seda</td>
<td>ethanolic</td>
<td>180-220</td>
<td>720-660</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Divinol Seda</td>
<td>ethanolic</td>
<td>120-180</td>
<td>480-720</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Esbericum forte</td>
<td>ethanolic</td>
<td>250</td>
<td>500</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Helarium</td>
<td>ethanolic</td>
<td>255-285</td>
<td>765-855</td>
<td>0.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Helarium</td>
<td>ethanolic</td>
<td>208-250</td>
<td>416-500</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Herbaustain forte</td>
<td>ethanolic</td>
<td>135-225</td>
<td>405-675</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Kira</td>
<td>ethanolic</td>
<td>100-120</td>
<td>200-240</td>
<td>0.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>
2 From Plant to Extract

2.1 St John’s Wort (*Hypericum perforatum* L.): Botanical Information

St John’s Wort, *Hypericum perforatum* L., is one of the family of *Hypericaceae* (synonym *Guttiferae*). The perennial, leafy plant reaches a height of about 60 cm and has 5-petalled, yellow flowers dotted with black hypericin glands. A blood-red latex oozes from the glands when the flower is rubbed.

The flowers contain red hypericin

The leaves have a characteristic perforated appearance

The name St John’s Wort comes from the fact that the plant flowers around St John’s Day which falls on 24 June. The ovate-elliptical leaves are dotted with translucent oil glands. The plant’s perforated appearance led to the species name *perforatum*. The stem has two characteristic vertical strips.

St John’s Wort is native to all of Europe, west Asia, the Canary Islands and North Africa.

The part which is used medicinally is the herb, *Hyperici herba*, consisting of the aerial parts *Hypericum perforatum* L. harvested during the flowering season and then dried [16, 32, 48, 55, 56].
Fig. 1: St John’s Wort (*Hypericum perforatum* L.).
2.2 Historic Use

St John’s Wort is a very old medicinal plant which was used particularly in the treatment of external wounds and burns. Hippocrates and Paracelsus praised its healing powers including in the treatment of "mad fantasies". The plant was repeatedly described in the medieval herbals. Many of the indications are still relevant in folk medicine today [7, 32, 55].

The use of St John’s Wort has been well-documented and recognized continuously up to the present day. This is reflected in the monograph [6, 11]. St John’s Wort is known as an antidepressant used in the treatment of psychovegetative disturbances for exhaustion, nervous headaches, agitation, anxiety, lacklustre, melancholy and apathy as well as for secondary psychological climacteric symptoms. Because of its relaxing effect St John’s Wort can be used for problems of insomnia especially in elderly patients [9].

St John’s Wort is used as an astringent tannic drug in mouth washes for the treatment of gingivitis and as an antidiarrhoeal agent. It is used internally (as an infusion) for disorders of the gastrointestinal tract [48], e.g., disease of the gall-bladder and gastritis, but also in the treatment of bronchitis and asthma [16].
Further areas of use are bed-wetting, rheumatism and gout. Its use as a diuretic is attributed to its flavonoid content [9, 55, 56]. Its effectiveness as a vermicide is attributed to the phloroglucin derivatives. Procyanidine is thought to be the active ingredient in the treatment of dyspeptic complaints [24].

2.3 Chemistry of the Plant Substances

St John’s Wort (*Hyperici herba*) contains several groups of substances. They are identified and quantified according to modern scientific analytical methods [8, 13, 29, 30, 33, 49].

The naphthodianthrones hypericin and pseudo-hypericin are characteristic substances of St John’s Wort and of pharmacological interest.

<table>
<thead>
<tr>
<th>Hypericin</th>
<th>Pseudohypericin</th>
</tr>
</thead>
</table>

Fig. 2: Hypericin and pseudohypericin found in St John’s Wort (*Hyperici herba*) [39].

The following table provides an overview of the whole spectrum.
Tab. 2: Substances found in St John’s Wort [4, 9, 16, 22, 39, 48, 56].

<table>
<thead>
<tr>
<th>Active and Other Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>• essential oil (0.05 - 0.3 %, n-alkannin, α-pinene, cineole)</td>
</tr>
<tr>
<td>• anthraquinone (skyrine)</td>
</tr>
<tr>
<td>• carotenoids (epoxyxanthophyll)</td>
</tr>
<tr>
<td>• cumarin (umbelliferone, scopoletin)</td>
</tr>
<tr>
<td>• flavonoids (0.5 - 1.0 %, flavonols, flavonoglucosides and biflavones including hyperoside and rutin)</td>
</tr>
<tr>
<td>• naphthodianthrones (0.1 - 0.3 %, including up to 80 or 90 % hypericin and pseudohypericin)</td>
</tr>
<tr>
<td>• carbolic acids (including chlorogenic acid, caffeic acid, ferulic acid, gentisic acid)</td>
</tr>
<tr>
<td>• phloroglucins (up to 3 % hyperforin)</td>
</tr>
<tr>
<td>• phytosterol</td>
</tr>
<tr>
<td>• proanthocyanidins (circa 10 % catechin tannins)</td>
</tr>
<tr>
<td>• wax (paraffins and wax alcohols)</td>
</tr>
<tr>
<td>• xanthones (mangostin)</td>
</tr>
</tbody>
</table>

Hypericin is considered the main substance of St John’s Wort

2.4 Preparation of the Extract and Quality Assurance

The plant material used for EUROMED Hypericum extract originates primarily from cultivations. An agreement with the suppliers is established in order to fix the conditions of cultivation, harvest, drying and storage, which assure the quality of the product.

Previous agreements with the suppliers about controls of the drug
Herbal Extracts Series 1. Hypericum

St John’s Wort extract is formed by many substance groups the individual active ingredients of which are largely known. The hypericins are considered to be the main characteristic active substances. The level of the hypericin and pseudohypericin is measured experimentally in order to optimize the production process and to assure quality of Hypericum extracts [36, 53].

When the plant material arrives at EUROMED an exhaustive control of the raw material is carried out according to the methods included in the current pharmacopoeia [8], paying special attention to the hypericin content in order to assure the quality of the final product.

Furthermore, EUROMED evaluates the eventual contamination of the drug; in doing so, the company assures that the limits fixed by the international norms or literature are not surpassed.


Aflatoxins: the contamination with these mycotoxins is controlled by legal limits worldwide

Heavy metals: the contamination with heavy metals is controlled by atomic absorption spectrophotometry

Microbiology: in compliance with the limits established in Ph. Eur. 3rd ed., 5.1.4 (category 4B), (1997)
Only high-quality raw plant material chosen according to the strictest criteria is selected. The extraction process is carried out using methods which avoid unnecessary damage and with continuous in-process checks in order to guarantee the quality, e.g. the HPLC (Fig. 3).

Fig. 3: HPLC-profile of *Hypericum perforatum* extract [4].

*Hypericum* extract from EUROMED satisfies the highest standards of quality thus enabling it to meet the requirements for the effectiveness and safe use of the medication.
2.5 Standardisation

**Consistent quality**

The consistent quality of the EUROMED Hypericum extract is guaranteed by the standardized production process.

**An extract of the whole herb is used**

Hypericin is the main substance of St John’s Wort with which the uptake and elimination of Hypericum extract can be determined. Other substances apart from hypericin, however, are also responsible for the effectiveness of the extract such as, for instance, hyperforin, the flavonoids, xanthone and the essential oil. For this reason the extract is taken from the whole of Hyperici herba.
3 Depressive States

Depression is the most common psychiatric disorder [18]. About 3 - 5 % of the global population (well over 100 million people) suffer from depressive mood disturbances requiring treatment. Up to 19% of patients seeking medical help suffer from symptoms of depression [5]. More than 90 % of the patients suffering from depression are treated by medical practitioners rather than clinics [52].

Every fourth adult suffers at least once in their lives from severe depression, women being more affected than men. There are four main kinds of depression [47]:

- reactive depression, brought on, for example, by unemployment or the loss of a partner
- endogenous depression, which develops for no apparent reason from within
- endoreactive depression, a mixture of endogenous and reactive depression
- neurotic depression, which can be characterized as abnormal behaviour within the framework of intrapsychic tensions

A deficiency of catecholamines (e. g., noradrenaline) or serotonin to specific receptors in the CNS is believed to be the cause of depression [57].

There is a large range of psychological and physical symptoms of depression (Tab. 3) [47]:
Tab. 3: Symptoms of Depression [47].

<table>
<thead>
<tr>
<th>Psychological Symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• anxiety</td>
</tr>
<tr>
<td>• agitation</td>
</tr>
<tr>
<td>• poor memory and lack of concentration</td>
</tr>
<tr>
<td>• feelings of hopelessness</td>
</tr>
<tr>
<td>• apathy and indecisiveness</td>
</tr>
<tr>
<td>• reduction in drive</td>
</tr>
<tr>
<td>• melancholy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• sleeplessness</td>
</tr>
<tr>
<td>• loss of appetite</td>
</tr>
<tr>
<td>• tightness in the chest</td>
</tr>
<tr>
<td>• dry mouth</td>
</tr>
<tr>
<td>• impaired potency</td>
</tr>
<tr>
<td>• constipation</td>
</tr>
</tbody>
</table>

According to WIECK the depression causes feelings of guilt, anxiety and melancholy [44]:

Fig. 4: Diagram of depression according to WIECK. The patient expresses feelings of melancholy in association with the present linked with guilt about the past and anxiety about the future [44].
However, about a third of depressions respond poorly or not at all to treatment with synthetic drugs (therapeutically resistance depression) [2].

In the past, unwelcome cholinergic side-effects have been observed, in particular to tricyclic antidepressants in non-hospitalized patients, such as dryness of the mouth and difficulty in focusing, disturbances of the cardiovascular and central nervous systems. Within 14 days almost half of the patients treated had their effective dosage reduced or completely stopped. The potential danger at the workplace and in traffic as well as interaction with alcohol reduced the compliance with tricyclic antidepressants [1, 5, 47].

Nowadays, less and less patients are prepared to accept undesirable side-effects and expect to be prescribed drugs which are both effective and carry a low risk when taken over a long period [21]. Therapeutic treatment with St John’s Wort extract has no cholinergic or sedative side-effects so that neither driving or operating machines at work is not effected [59].
St John’s Wort has rightly become a standard medication in the treatment of depression and is well regarded by medical practitioners. The emphasis of the treatment is on the symptomatic and reactive depressions as well as on neurotic depression and psychovegetative syndrome. It should be remembered that these conditions are chronic and always necessitate long-term therapy. The positive effect of St John’s Wort on patients’ moods does not become evident for at least two to three weeks. Therapy should last for at least two to three months [1, 55].
4 Pharmacology

4.1 Antidepressant Effect

The antidepressant effect of St John’s Wort extract is not based on a single mechanism but rather, as is the case with many herbal remedies, is brought about by many different mechanisms.

4.1.1 Blocking the Resorption of Serotonin

The effect observed under the influence of Hypericum extract of the reduced availability of serotonin receptors and the associated possible resorption of the neurotransmitter serotonin into the cell could be an example of the antidepressant mechanism of the Hypericum extract. Using fluorescent microscopic methods to examine them, nerve cells which had been incubated with Hypericum extract displayed significantly less serotonin receptors on their surface then before incubation [34].

Studies using synaptosomes from rat brains showed that with a concentration of Hypericum extract of 6.2 µg/ml the serotonin resorption was reduced by 50 % (IC$_{50}$ value). This has been taken to mean that the antidepressant activity of the Hypericum extract is due to a blocking of the serotonin resorption by post-synaptic receptors (see following graph) [37].
Fig. 5: Uptake of $^3$H-serotonin (5-HT) by rat synaptosomes as a function of incubation time. Five experiments for each value were performed. The results have been corrected with respect to the passive transport of serotonin [37].

Fig. 6: Effect of Hypericum extract on the $^3$H-serotonin (5-HT) uptake by rat synaptosomes. The incubation period after addition of serotonin was 20 min. Five experiments for each value were performed.
The hypericins are said to have a further effect on the serotonin metabolism. They are supposed to work by increasing light utilization and influencing the serotonin-melatonin metabolism. As a colour pigment hypericin absorbs light in the long-wave section of the light spectrum and thus helps the patient to use whatever light is available more effectively, which often leads to a lifting of depressive moods. Hypericin also raises the concentration of melatonin, a hormone which is formed in the pineal gland of the brain out of serotonin and has a sleep-regulating function [47]. In addition the hypericins are said to have an antiviral effect [24].

4.1.2 Slight Blocking of the Monoamine oxidase (MAO)

The enzyme monoamine oxidase (MAO) is to a large part responsible for the breakdown of the neurotransmitter noradrenalin. The initial strengthening of noradrenalin probably leads to an adaptive alteration of the receptor systems localized on the postsynaptic side and to transduction mechanisms. Since MAO is also responsible for the intraneuronal breakdown of serotonin, MAO blockers at the serotoninergic synapsis lead to similar effects as at noradrenergic synapsis. An in vitro model of the proof of the effectiveness of the Hypericum extract showed a slight blocking effect of the resorption of the neurotransmitter. It was also shown that hypericin alone cannot be responsible for the effect [35].
Fractionated extracts have, however, shown both *in vitro* and *ex vivo* that flavones and flavonols (e.g. quercetin and quercetrin) are MAO A-blockers while the cumarin fraction blocks MAO-B [3, 16, 24]. A molecular modelling study has shown that MAO-blocking effects are conceivable for the flavonoids contained in *Hypericum* but that this is unlikely to be a mechanism of hypericin [23]. The side-effects which are sometimes associated with strong MAO blockers do not occur with *Hypericum* Extract.

### 4.1.3 Blocking the Catechol-O-methyl-transferase (COMT)

A further enzyme involved in the breakdown of the neurotransmitter is catechol-O-methyltransferase (COMT). *Hypericum*, an extract made from the whole herb blocks COMT in a concentration of $10^{-4}$ M. The COMT-blocking fraction contains for the most part flavonols and xanthone [51]. In other *in vitro* experiments quercetin and rutoside were also shown to have a blocking effect [16].

### 4.1.4 Modulation of Cytokine Release

A modulation of the release of cytokine has also been discussed as having a further antidepressant effect. Cytokines (including interleukins) are important components in the psychoneuroimmuno-endocrinal communication between cells outside the immune system, in particular the nervous system.
Hypericum extract acts in vitro as a direct modulator of interleukin-6. In vivo it was thus possible to indirectly control the secretion of the corticotropin releasing hormone (CRH) with Hypericum extract and to activate its antidepressant effect using this mechanism [4, 51].

4.2 Pharmacokinetics

The extract of St John’s Wort is a complex compound mixture. Pharmacokinetic experiments on the extract of the whole herb are, therefore, difficult and have primarily been carried out for the main substances hypericin and pseudohypericin [46].

Resorption occurs quickly and in concentrations proportional to the dose administered. The maximum concentration $c_{\text{max}}$ of 4.3 ng/ml was achieved after $t_{\text{max}} = 2.5$ hours. After the resorption phase the exponential elimination followed with a half-life value of 6 hours [54].

Fig. 7: Hypericin concentration in the plasma after the administration of 600 mg Hypericum extract. Mean of 12 test subjects [54].
5 Toxicology

Phototoxic effect is unlikely

Hypericin is responsible for the photodynamic effect and the hypericism seen in grazing animals [38]. Studies have shown, however, that the usual therapeutic doses of *Hypericum* extracts used are below the threshold of phototoxicity by a factor of between 30 and 50 [45].
6 Clinical Pharmacology

6.1 Influence on Evoked Potentials and Resting EEG

In double-blind trials using placebos the neurophysiological effect profile and the effects of the Hypericum extract on the subjective symptoms as well as on the cognitive performance parameters were studied in healthy volunteers. Pharmaco-EEG-examinations (electro-encephalo-graphy) were carried out and both the acoustic and visually evoked potentials deduced at two week intervals.

The pharmacodynamic trials demonstrated that a neurophysiological profile similar to that of a „classical“ antidepressant such as imipramine or maprotiline, which have relaxing and CNS activating characteristics, was achieved with high doses of St John’s Wort extract (reduction in the alpha spectrum accompanied by an increase in the slower theta and faster beta waves = dissociative frequency displacement). Along with its mood-enhancing characteristics St John’s Wort extract also has a positive effect on cognitive abilities [26, 28].
Fig. 8: Effect on resting EEGs after 6 weeks of treatment with the verum and the placebo. Such changes are typical for tricyclic antidepressants [26].

The effects of Hypericum extract (as available from EUROMED) in comparison with those brought about by maprotilin were looked at in a randomized study with 24 healthy trial volunteers. In the resting EEG opposite effects were seen in the theta area for the two drugs while very similar changes were seen in the alpha and beta areas. Measurement of evoked potentials in the theta and beta range supported these findings. The results point to a general improving effect on the cognitive abilities during treatment with Hypericum extract [27].
7 Proof of Clinical Effectiveness

7.1 Meta-analysis of the Clinical Trials of the Use of St John’s Wort Extract for Psychovegetative Complaints

The effectiveness of Hypericum extract was demonstrated in a meta-analysis and systematic overview of over 20 randomized trials including patients with mainly mild or moderately severe depressive disorders. 14 placebo-controlled trials showed the significant superiority of St John’s Wort extract over the placebo. 6 studies describe St John’s Wort extract as having the same antidepressant effect as standard medication.

The trials used various methods to measure and rate treatment effects. The most consistently used instruments were the HAMILTON depression scale (HAMD) and the clinical global impressions index (CGI).

The HAMILTON depression scale is an observer-rated scale focusing mainly on somatic symptoms including 17 items. The clinical global impressions index is an observer-rated instrument with three items (severity of illness, global improvement and an efficacy index) [31].
7.2 Clinical Trials with Placebos

In Section 7.1 on meta-analysis it was stated that 14 placebo-controlled double-blind trials demonstrated the effectiveness of St John’s Wort. Some of these trials are described below.

In a randomized, placebo-controlled double-blind trial 39 patients suffering from depressive moods with accompanying psychovisual symptoms in the form of a masked depression were treated for four weeks. The group receiving the verum were given 300 mg St John’s Wort extract three times daily. 70% of the patients showed no symptoms after 4 weeks. Symptoms which reacted particularly well to treatment were lacklustre, exhaustion, fatigue and sleep problems [25].

A multi-centre, randomized, double-blind, placebo-controlled trial with 102 out-patients suffering from a Major depression of mild to moderate severity according to DSM-III-R demonstrated the effectiveness of a *Hypericum* extract (900 mg/day). The treatment lasted 4 weeks, with all the patients being given the verum subsequent to the trial. The total score on the HAMILTON depression scale (HAMD) had dropped more significantly in the verum group after 4 weeks than in the placebo group. Significant differences were also measured on von ZERSSENS depression scale (D-S). The administration of the verum over a period of 2 weeks after completion of the placebo phase led to a reduction in the symptoms. These results thus confirmed the results of earlier trials [14, 15].
Fig. 9: HAMILTON depression scale (HAMD). In the group treated with the verum the score value dropped within 4 weeks from 21.0 to 8.9 and from 20.4 to 14.4 in the placebo group. The differences between the verum and the placebo groups after 2 and 4 weeks were highly significant (p<0.001 respectively). In the 5th and 6th week during which period both groups were given the verum a marked improvement in the original placebo group was seen [14].

Fig. 10: von ZERSSENS depression scale (D-S). After 4 weeks of treatment with the verum the levels considered as the norm for healthy volunteers were reached (mean value and standard deviation). In this case too subsequent treatment of the placebo group with the verum (weeks 5 and 6) led to a reduction in symptoms, which with reference to the scale value correspond at least to the verum group (weeks 1 and 2) [14].
In a further randomized, double-blind, placebo-controlled trial in three practices of psychiatrists, internists and general practitioners, the effectiveness of a Hypericum extract in the treatment of mild to moderately severe depressions was documented. 105 non-hospitalized patients suffering from neurotic depression or short bouts of depressive mood changes were treated with 900 mg/day of St John’s Wort extract or with a placebo for a duration of 4 weeks. Significant changes were reported in the trial drug/placebo comparison for the symptoms of depressives moods (feelings of melancholy, hopelessness, helplessness, low self-esteem, see Fig. 11), for the psychological anxiety and the symptoms "difficulty in getting to sleep", "heart complaints", "exhaustion" and "headaches" [21].

Fig. 11: Depressive moods (feelings of melancholy, hopelessness, helplessness, low self-esteem) according to the HAMILTON scale. Statistically significant improvement in the depressive moods in the verum group after 4 weeks of treatment [21].
The St John’s Wort extract provides doctors treating patients suffering from depression with an efficient herbal remedy which is well accepted by them. It is a medication which has shown clear superiority over placebos in placebo-controlled double-blind trials [17].

7.3 A Comparison of Clinical Trials and Standard Conditions

In a double-blind comparative trial 135 depressive patients were treated in 20 trial centres. This trial included patients with diagnoses ranging from typical depression with single episodes and those with repetitive episodes, depressive neurosis and adjustment disorders with depressive mood alteration as defined according to DSM-III-R. The dosage used was 3 x 300 mg *Hypericum* extract or 3 x 25 mg imipramine daily over a period of 6 weeks. The reference criteria used were the HAMILTON depression scale (HAMD), von ZERSSENS depression scale (D-S) and the clinical global impressions index (CGI).

A similar reduction in the HAMILTON-Scores and in the statistical D-S values occurred in both treatment groups. The evaluation of the CGI produced similar results for both groups. Less and milder side-effects were reported in the *Hypericum* group than in the imipramine group [52].
Comparison of the effectiveness and tolerability of a *Hypericum* extract and maprotiline was carried out in a multi-centre, randomized, double-blind trial with 102 depressive patients. Over a period of 4 weeks treatment was administered with 3 x 300 mg *Hypericum* extract or 3 x 25 mg maprotiline. A similar level of effectiveness was reported after 4 weeks (Fig. 12). Less side-effects were reported in the *Hypericum* group [19].

Fig. 12: Mean value of the total score on the HAMILTON depression scale. There was a drop of around 50 % in both trial groups during the 4 week period of treatment [19].

A variety of more recent double-blind trials demonstrate the clinical effectiveness of high doses of St John’s Wort preparations in the symptomatic treatment of depression. It has been shown to be more effective than a placebo and when compared with standard medication to be just as effective. When the mild or non-existent side-effects are taken into account St John’s Wort extract must be seen as medication of first choice in the treatment of mild and moderately severe depression [2, 10].
7.4 Drug Monitoring Trials

In an observation study of its clinical use, the effectiveness and tolerability of a 5-week course of treatment with a St John’s Wort preparation was demonstrated in subjects suffering from psychological depressive states. Typical psychological and somatic symptoms were reduced both in their severity and frequency [12].

A drug monitoring trial was carried out in association with the treatment of over 1000 patients under the care of a total of 270 medical practitioners. The patients were suffering from mild to moderately severe depression and were treated over a period of 4 weeks. The effectiveness and assessment of the tolerability of the St John’s Wort preparation were standardized using, for example, the HAMILTON depression scale (HAMD) and von ZERSSENS scale (D-S scale). After 4 weeks of treatment a marked clinical reduction in the symptoms was observed. More than three quarters of the patients exhibited no further symptoms of depression. In 90% of the cases tolerability was positively assessed [1].

Symptoms recede

Depressions recede
Effectiveness and tolerability of a 4-week course of treatment with *Hypericum* extract administered to 3259 patients was monitored by 663 medical practitioners. The typical symptoms receded in both frequency and severity by about 50%. Around 80% of the patients improved or were completely symptom-free during treatment. Only 2.4% of the patients complained of side-effects [59].

Fig. 13: Absolute frequency of the specific symptoms in 3259 depressive patients before and after treatment with *Hypericum* extract [59].
7.5 Effect on Patients’ Responses

A double-blind trial including a placebo group was carried out on the medically measurable traffic responses of 60 patients. *Hypericum* extract was shown to have no negative effect on responses [41, 43].

In a placebo-controlled double-blind trial using the cross-over design, the interaction of *Hypericum* extract with alcohol during treatment was tested. No such interaction was observed. This finding is of particular importance for non-hospitalized patients on antidepressant therapy who continue to work and drive during treatment [42].

St John’s Wort does not have a sedative effect. It leads instead to mild relaxation in the patient while at the same time activity and attention are increased.
7.6 Therapeutic Safety

**High level of therapeutic safety**

*Hypericum* extract is notable for its particularly high level of clinical safety. To date no acute cases of *Hypericum* extract poisoning have been reported [16]. *Hypericum* extract is a particularly safe form of treatment for patients diagnosed as having depression which could lead to attempted suicide.

**High level of compliance**

Particular emphasis should be put on the high level tolerability of St John’s Wort preparations which leads to a high level of treatment compliance because of the almost total absence of side-effects. This absence of sides-effects means that here is also no impairment of function when operating machines or when driving in traffic [40].

In contrast to many synthetic antidepressants the extract of St John’s Wort does not have a sedative effect and can be recommended without restrictions for patients who are working and all patients who require full concentration for driving and for operating machines [44]. The mood-enhancing St John’s Wort does not carry with it a danger of addiction, its effect is not increased by alcohol and it well accepted by patients.

**No danger of addiction**
8 Bibliography

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39
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