
Review

Current St. John’s wort research from mode of action to clinical efficacy

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Abstract

Preparations from St. John’s wort extracts are used in the treatment of depression in many countries and represent an accepted alternative to synthetic antidepressants or behavioural therapy. St. John’s wort extracts are therefore used in a therapeutic area which extends well beyond the traditional field of herbal medicine. The current status of preclinical and clinical research is summarised. St. John’s wort extract has a clear inhibitory effect on the neuronal uptake not only of serotonin, noradrenaline, and dopamine but also of gamma-aminobutyric acid (GABA) and 1-glutamate. No other antidepressant shows an approximately equally broad inhibitory profile. In good agreement with the effects in various biochemical models of antidepressant action, many effects in a number of behavioural pharmacology models of antidepressant efficacy could also be demonstrated for St. John’s wort extract. Similar doses of John’s wort also cause changes in the above-mentioned neurotransmitter systems in the brain. Out of all individual substances of St. John’s wort only hyperforin and its structural analogue adhyperforin inhibit the re-uptake of the investigated neurotransmitters. However, hyperforin does not act as a competitive inhibitor at the transmitter binding sites of the transporter proteins but it affects the sodium gradient which then leads to an inhibition of uptake. The broad spectrum of action which characterises St. John’s wort extracts has only been described for the pure substance hyperforin. Over the past year a number of good clinical studies have been carried out which confirm the efficacy and tolerability of St. John’s wort extracts in mild depressive disorders, even if the therapeutic efficacy has recently been questioned by an American study. All studies have confirmed the good tolerability of St. John’s wort extract and the very low frequency of adverse events. However, some drug interactions have been found to occur with St. John’s wort extract, a number of which are of clinical relevance. In summary, pharmacological activity and therapeutic efficacy of St. John’s wort extract as an antidepressant are supported by a large number of scientific publications. Within the wide range of components in St. John’s wort extract, hyperforin plays an important, if not an outstanding role.

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Keywords: St. John’s wort; Pharmacological properties; Antidepressant efficacy; Hyperforin; Side effect profile

1. Introduction

Preparations from St. John’s wort extracts have become widely used in the treatment of depression in many countries and represent an accepted alternative to synthetic antidepressants or behavioural therapy, particularly for mild to moderate disorders [1–6]. St. John’s wort extract preparations are therefore not only used for a common and potentially life-threatening disease (risk of suicide) but also for patients suffering enormously and for a disorder which is extremely expensive for our insurance system (medical consultations, medication, days off work, sick leave). St. John’s wort extracts are therefore used in a therapeutic area which extends well beyond the traditional field of herbal medicine. In view of this, it appears completely appropriate to require that the use of St. John’s wort preparations should comply with the criteria of rational drug therapy, which are defined in terms of activity, efficacy and safety by the legal authorities. The current status is summarised in the present communication.

2. The role of noradrenaline and serotonin for the mechanism of action of antidepressants

Today, it is known that almost all antidepressants influence the synaptic communication of the neurotransmitters serotonin and noradrenaline in the CNS, although different biochemical pathways are involved. The majority of antidepressants lead, at least initially, to an increased availability of noradrenaline and serotonin at the respective synapses (Fig. 1). One possible mode of action is the inhibition of the intra- and extraneuronal enzyme monoamine oxidase (MAO), a pathway which is exploited by the MAO inhibitors. By this means, the break-down of both neurotransmitters is retarded and their concentration at the contact sites

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The biochemical mechanism of action of St. John’s wort extract exhibits similarities to that of other antidepressants. Many synthetic antidepressants lead to an increase in concentration of the two neurotransmitters noradrenaline and serotonin in the synapses (contact sites between nerve cells) of the brain by, at least initially, influencing different mechanisms (inhibition of neuronal noradrenaline or serotonin re-uptake, inhibition of monoamine oxidase-A, inhibition of pre-synaptic α2 receptors). As a consequence, adaptive changes in the post-synaptic receptor system take place, which occur over the same period as the antidepressant action. St. John’s wort also blocks both transport systems (mainly by means of the active ingredient hyperforin) and leads to changes in the serotoninergic (5-HT1A and 5-HT2A receptors) and noradrenergic (noradrenaline) synapses (Fig. 1).

Earlier investigations, which assumed an inhibitory effect of St. John’s wort extract on the monoamine oxidase A enzyme (Fig. 1), and considered the extract as a herbal MAO inhibitor, could not be confirmed in our studies [7].

The most important biochemical mechanism of antidepressant activity relates to the classic tricyclic antidepressants (TCA) but is also valid for almost all old and new antidepressants. The TCAs inhibit the transport proteins which return the neurotransmitters released into the synapse back to the pre-synaptic section of the synaptic contact (Fig. 1). The selective serotonin re-uptake inhibitors have the same effect, but these substances are only effective for serotonin transporters and not for noradrenaline transporters.

Adaptive changes in receptor structure take place in the nerve cells receiving the transmitter signal, probably as a consequence of the increasing concentrations of both neurotransmitters in the synaptic gap (Fig. 1). Important examples of such adaptive changes are the reduction in density of α2-receptors at the noradrenergic synapse or the decrease in density of 5-HT2A-receptors or the increase in density of the 5-HT1A-receptors in the serotoninergic synapse, as shown by arrows in Fig. 1. As the time course of the adaptive changes correlates with the slowly developing antidepressant efficacy of all antidepressants (2–3 weeks), it is assumed that these changes are an important aspect of the general mechanism of antidepressant action.

3. St. John’s wort extract has a broad spectrum of action

St. John’s wort extract has a clear inhibitory effect on the synaptosomal uptake not only of serotonin, with a mean inhibitory concentration of 2 μg/ml (Table 1). To our surprise, and in clear contrast to the characteristics of all other antidepressants, we found similar inhibitory effects on the synaptosomal uptake also not only for noradrenaline and dopamine but also of gamma-aminobutyric acid (GABA) and L-glutamate [8] (Table 1). From the comparative data (Table 1), it can be seen that none of the known standard antidepressants has such a broad spectrum of action as that shown by St. John’s wort, which inhibits all systems with approximately the same affinity. All other antidepressants are either specific to one system only or show overlapping inhibitory effects on maximal two of the systems investigated. We know of no other antidepressant that shows an approximately equal inhibitory activity on the synaptosomal uptake of all five neurotransmitters.
Table 1  
Mean inhibitory concentration (IC₅₀) of several antidepressants, hyperforin and of a St. John’s wort extract on the synaptosomal uptake of various neurotransmitters

<table>
<thead>
<tr>
<th>Substance</th>
<th>Serotonin uptake</th>
<th>Dopamine uptake</th>
<th>Noradrenaline uptake</th>
<th>GABA uptake</th>
<th>Glutamate uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>imipramine</td>
<td>21</td>
<td>&gt;1000</td>
<td>21</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>clomipramine</td>
<td>1</td>
<td>&gt;1000</td>
<td>14</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>desipramine</td>
<td>207</td>
<td>&gt;1000</td>
<td>3</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>citalopram</td>
<td>1</td>
<td>&gt;1000</td>
<td>1</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>hyperforin</td>
<td>205</td>
<td>102</td>
<td>80</td>
<td>184</td>
<td>143</td>
</tr>
<tr>
<td>St. John’s wort extract</td>
<td>2²</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

²About 2% hyperforin.

Table 2  
Behavioural pharmacology tests indicative of an antidepressant effect in man in which St. John’s wort extract was effective (after [25,47]).

<table>
<thead>
<tr>
<th>Test</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced swimming (Porsolt’s)</td>
<td>Yes</td>
</tr>
<tr>
<td>Tail suspension test</td>
<td>Yes</td>
</tr>
<tr>
<td>Learned helplessness test</td>
<td>Yes</td>
</tr>
<tr>
<td>Reserpine test</td>
<td>Yes</td>
</tr>
<tr>
<td>Water wheel test</td>
<td>Yes</td>
</tr>
<tr>
<td>Aggressiveness in socially isolated mice</td>
<td>Yes</td>
</tr>
<tr>
<td>Escape deficit model</td>
<td>Yes</td>
</tr>
<tr>
<td>Mild chronic stress</td>
<td>Yes</td>
</tr>
</tbody>
</table>

4. Influence on neurotransmission in vivo

For the understanding of St. John’s wort extract as an antidepressant it is particularly significant that a number of authors also found changes in the central concentrations of the three neurotransmitters, noradrenaline, serotonin and dopamine or their metabolites, in the CNS of experimental animals after acute or chronic treatment. As for the synthetic antidepressants, the data are not uniform, but different effects are observed depending on the dose, the duration of treatment and the brain area investigated [9–12].

In general, these findings confirm that doses of St. John’s wort (see Table 2) that are active in biochemical models of antidepressant action also cause changes in receptor density given in the following chapter, a link between biochemical in vitro investigations and in vivo changes typical of antidepressants in the brain of experimental animals is established.

5. Effects on the density of β- and 5-HT₂-receptors

We could also confirm an influence on noradrenergic and serotoninergic mechanisms in vivo by showing that sub-chronic treatment of rats with imipramine or St. John’s wort extract resulted in a significant reduction in β-receptor density in the frontal cortex [7]. These findings obtained with the rat selective ligand [³H]-DHA were recently confirmed using a β-selective radioligand ([³H]-CGP 1277) [13].

If we treated rats with imipramine under otherwise identical conditions, we could also show a significant down-regulation of the 5-HT₂-receptors in the frontal cortex [7]. The same treatment with St. John’s wort extract did not lead to a decrease in the 5-HT₂-receptor density in the frontal cortex, however, but to a significant increase in the number of 5-HT₂-receptors [7]. This phenomenon is usually not seen for antidepressants but has been reported for electro-convulsive therapy, the “Ultima Ratio” in the treatment of depression, which often helps when nothing else does. St. John’s wort extract therefore shows biochemical effects on central noradrenergic and serotoninergic synapses which are analogous to those of other antidepressants or antidepressant therapies (Fig. 1).

6. Behavioural pharmacology studies

In good agreement with the effects in various biochemical models of antidepressant action, many effects in a number of behavioural pharmacology models of antidepressant efficacy could also be demonstrated for St. John’s wort extract by a number of different working groups. These models included the reversal of several behaviour patterns induced by reserpine, elimination of the immobilisation time in the Porsolt test and reversal of helpless behaviour in the model of learned helplessness (Table 2).

It is of great significance that evidence for activity of St. John’s wort extract has been shown in a series of different behavioural pharmacology models, all of which are to some extent indicative of an antidepressant action in man. However, none of these models alone is sufficiently representative, as false positive and false negative substances appear time and again.

This is unfortunately also true of the immobilisation test (Porsolt test), which is often used because it is relatively easy
to perform. This test was originally developed for short-term applications. Under these conditions, tricyclic antidepressants and St. John’s wort extract are efficacious, for example. However, today’s leading antidepressants in the specific serotonin re-uptake inhibitor (SSRI) group are not. Only when a longer treatment period is used (e.g. the 9 days routinely used by us), can the efficacy of the SSRI be shown in this model, and the effects for St. John’s wort extract become even more pronounced [14].

Only when different experimental models are used, an acceptable prediction of the therapeutic efficacy in patients can be made in some measure from preclinical experiments. This is true for St. John’s wort extracts.

7. Hyperforin, a “broad-band re-uptake inhibitor”

The marked MAO-A inhibitory effect of St. John’s wort extract, which was subsequently never confirmed, was originally associated with hypericin, a component important for the phototoxic effect. Likewise, MAO inhibition could not be confirmed for hypericin [7]. Furthermore, in our investigations on synaptosomal uptake of serotonin, noradrenaline, dopamine and GABA, pure hypericin was not effective [15].

Recently, exciting new aspects with regard to the molecular mode of action of hyperforin have also emerged. Hyperforin does not act as a competitive inhibitor at the transmitter binding sites of the transporter proteins like all the other antidepressants [17,19–23] but shows a completely novel mechanism of action. The driving force of all the high-affinity neuronal neurotransmitter transport mechanisms mentioned is the sodium gradient between the extracellular and low intracellular sodium concentrations. All transport proteins are driven by this sodium gradient in such a manner that the neurotransmitter is practically pushed into the cell through co-binding of sodium ions. For hyperforin, we could show that it reduces the sodium gradient by the activation of a not yet characterised sodium conductivity mechanism which then leads to an inhibition of uptake [20,21]. The fact that the sodium gradient is relevant for all these transporter uptake mechanisms also explains the unusual finding, mentioned already above, that hyperforin inhibits the uptake of a large number of neurotransmitters to about the same degree [8]. In addition, after acute or repeated administration of hyperforin in experimental animals, biochemical changes could be found in the brain that confirm in vivo effects on the neurotransmitter systems which are typical for antidepressants (e.g. β down-regulation or changes in transmitter or metabolite concentrations) [10,11,16].

8. Molecular mechanism of action of hyperforin

Recently, exciting new aspects with regard to the molecular mode of action of hyperforin have also emerged. Hyperforin does not act as a competitive inhibitor at the sodium gradient by the activation of a not yet characterised sodium conductivity mechanism which then leads to an inhibition of uptake [20,21]. The fact that the sodium gradient is relevant for all these transporter uptake mechanisms also explains the unusual finding, mentioned already above, that hyperforin inhibits the uptake of a large number of neurotransmitters to about the same degree [8]. In addition, after acute or repeated administration of hyperforin in experimental animals, biochemical changes could be found in the brain that confirm in vivo effects on the neurotransmitter systems which are typical for antidepressants (e.g. β down-regulation or changes in transmitter or metabolite concentrations) [10,11,16].

9. Effects of hyperforin on behaviour

In behavioural pharmacology experiments, the dominating role of hyperforin could also be demonstrated by a number of different authors (Table 3). In our initial findings, the activity of St. John’s wort extract in the immobilisation and the learned helpless paradigms were largely determined by hyperforin [8]. Similar findings have been reported by us and many other groups for many other behavioural models [23–26]. If hyperforin is removed from the extract, activity can be still registered in the Porsolt test under our conditions, which is an indication of other active ingredients, but the effect of the hyperforin-free extract was not as marked [14].

In other models, e.g. the reserpine test, a classic model particularly for tricyclic antidepressants, hyperforin-free extract is not effective [14]. No adequate effect could be demonstrated for hyperforin-free extracts in a number of other animal experimental models to date (Table 4).

Table 3 Pharmacological models in which the effect was depending on hyperforin (data from [8,10,11,14–17,24–26,45,46,48])

<table>
<thead>
<tr>
<th>Pharmacological model</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learned helplessness</td>
<td>Porsolt test (under certain conditions)</td>
</tr>
<tr>
<td>Passive avoidance learning (cognition)</td>
<td>Elevated plus maze (anxiolysis) (hypericin is ineffective)</td>
</tr>
<tr>
<td>Avoidance deficit model</td>
<td>Increase in extracellular serotonin and dopamine concentrations in micro-dialysis experiment</td>
</tr>
<tr>
<td>Release of growth hormone</td>
<td></td>
</tr>
</tbody>
</table>
2. Cognition improvement (passive avoidance learning) has been demonstrated for hyperforin (after [24,25,48,49]).

Beyond the actual antidepressant activity has so far only been comprehensively documented as those of hyperforin. In a study by Laakmann et al. [30], in which two St. John’s wort extracts with either high or low hyperforin content were tested against placebo in depressive patients, only the hyperforin-rich extract was more effective than placebo. These findings are in contrast to those of a clinical study with a different St. John’s wort extract, low in hyperforin which showed significant improvement in the placebo group was shown in this investigation, but the group was arithmetically slightly worse towards the end of the study [31]. This is such an unusual finding, that the validity of this study should at least be discussed. Two other studies have shown comparable therapeutic effects of low hyperforin St. John’s wort extract compared to imipramine or fluoxetine [32], but there were no placebo groups in these studies, which today is a general requirement for comparative studies [33]. Accordingly, no final conclusions can be drawn from those studies. Consequently, according to the current data, it might be possible that hyperforin-low St. John’s wort extracts may also show some therapeutic effect, although not as marked as that of hyperforin-rich extracts. Besides, for the synthetic antidepressants it is also assumed that substances with dual mechanisms of action have advantages compared to the pure serotonin or noradrenaline re-uptake inhibitors [34].

Furthermore, pharmacological activity in paradigms beyond the actual antidepressant activity has so far only been shown for hyperforin (Table 5). Anxiolytic effects in particular should be mentioned here. These also provide the link to modern antidepressants of the SSRI type, the efficacy of which has been well documented for different anxiety symptoms or anxiety states. St. John’s wort extracts containing hyperforin and pure hyperforin (but not hyperforin-free extracts) are also effective in the passive avoidance learning model. This indicates an improvement in learning and memory capacity rather than an antidepressant effect. Furthermore, we recently described an effect of hyperforin on the metabolism of the amyloid precursor protein molecule, which possibly indicates activation of a-secretase (Table 5).

### Table 4

<table>
<thead>
<tr>
<th>Pharmacological models in which hyperforin-free St. John’s wort extracts were not effective</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine test (depression)</td>
<td>[11, 14, 24, 25, 26]</td>
</tr>
<tr>
<td>Scopolamine test (depression)</td>
<td></td>
</tr>
<tr>
<td>Passive avoidance learning (cognition)</td>
<td></td>
</tr>
<tr>
<td>Increase in extracellular serotonin, GABA and glutamate concentrations</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>Pharmacological characteristics beyond depression, which so far have only been demonstrated for hyperforin (after [24, 25, 26])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pharmacology (related plus minus)</td>
</tr>
<tr>
<td>2. Cognition improvement (passive avoidance learning)</td>
</tr>
<tr>
<td>3. Increased APP processing (stimulation of a-secretase)</td>
</tr>
</tbody>
</table>

### 11. Clinical efficacy

Although the therapeutic use of St. John’s wort extracts first came from practice, the high acceptance, such as found today in Germany and a few other countries, can only be explained by the fact that over the past years a number of good clinical studies have been carried out which confirm
the efficacy and tolerability of St. John’s wort extracts in mild depressive disorders (for reviews [1–6]). The therapeutic efficacy has recently been questioned by an American study [35]. Thus, it appears necessary to summarise advantages and limitations of St. John’s wort extract in the treatment of depressive disorders on the basis of two newer clinical studies.

12. A comparison of two most recent clinical studies

The much quoted “negative” American study [35] represents a multicenter, randomised, double-blind, placebo-controlled study in which patients with an initial score on the Hamilton Depression Scale (HAMD) of at least 20 were included. Following a single-blind placebo run-in phase, the double-blind treatment study lasted 8 weeks. The primary assessment criterion was the HAMD, but a series of other self- and third-party assessment scales were investigated in addition.

The essential finding of this study revealed no difference in time course of the HAMD primary target criterion over the 8 weeks, as the placebo and St. John’s wort curves did not differ significantly. This also applied to the majority of other scales investigated. However, if the proportional distribution of responders (50% or higher improvement at end point) is considered, a numerical advantage of St. John’s wort extract compared to placebo was found, although not of statistical significance. In general, placebo response (14%) was exceptionally low. The situation was further strikingly different to the placebo response of 17% in the Shelton study. It is possible to speculate that the rating of the depressive illness in the Shelton study was relatively low. Additional analyses in the Lecrubier study with the sub-scale melancholia and the sub-scale anxiety and somatisation showed highly significant benefits of St. John’s wort extract treatment in both domains [42]. The Lecrubier study is therefore in agreement both with many other clinical studies on antidepressants, where the extremely high placebo response represents a considerable methodological problem [33,50], and with a series of other recently published placebo-controlled clinical studies on St. John’s wort extract of high methodological standard. It emphasises once again the exceptional position of the two American studies. This is also supported by a recent meta-analysis of clinical data obtained with hyperforin-rich St. John’s wort extracts indicating clinical efficacy over all symptoms of the depressive syndrome [38].

To sum up: certainly an interesting study, where the central statement, that St. John’s wort extracts in the dose used (usually 900 mg per day) is possibly not sufficiently effective for severely and chronically depressive patients, should be accepted. Apart from this, it is known that St. John’s wort extract is not the therapy of choice in cases of severe depressive illness. Most important, the indirect implication of this study that other antidepressant (e.g. SSRIs) would have been more effective is not confirmed. Even more, a most recent American study, were even slightly less severely and chronically ill depressant patients were included, failed to show therapeutic efficacy not only for St. John’s wort but also for the active comparator sertralin (a SSRIs) [36]. This shows, that patient selection in both studies was not only biased against the herbal but also against one of the mostly prescribed synthetic antidepressant as well.

A recently published placebo-controlled, double-blind study carried out in France by Lecrubier et al. [37] was of similar design. These patients also had baseline scores on the HAMD scale of somewhat over 20. There was a very clear placebo response, however, and a significant superiority of the St. John’s wort extract according to the HAMD scale at the end point of the study. The placebo response at the end of the 6-week therapy phase of over 40% is therefore strikingly different to the placebo response of 17% in the Shelton study. It is possible to speculate that the rating of the depressive illness in the Shelton study was relatively low. Additional analyses in the Lecrubier study with the sub-scale melancholia and the sub-scale anxiety and somatisation showed highly significant benefits of St. John’s wort extract treatment in both domains [42]. The Lecrubier study is therefore in agreement both with many other clinical studies on antidepressants, where the extremely high placebo response represents a considerable methodological problem [33,50], and with a series of other recently published placebo-controlled clinical studies on St. John’s wort extract of high methodological standard. It emphasises once again the exceptional position of the two American studies. This is also supported by a recent meta-analysis of clinical data obtained with hyperforin-rich St. John’s wort extracts indicating clinical efficacy over all symptoms of the depressive syndrome [38].

13. Tolerability and interactions

Both clinical studies mentioned in this review confirmed the good tolerability of St. John’s wort extract and the very low frequency of adverse events. This emphasises once more the undisputed advantage of St. John’s wort in the outpatient treatment of depressive disorders as mentioned in Section 1 [1–6].

Recently, the assessment of St. John’s wort extract as a generally unproblematic therapy had to be revised in certain respects, as various drug interactions have been found to occur with St. John’s wort extracts, a number of which are...
of clinical relevance. This topic has been presented in a number of recent publications [39–41,43,44], so that only a short summary and assessment will be given here.

On co-medication with St. John’s wort, a reduction in the plasma levels of a number of other medications has been reported, although clinical consequences were not reported in every case. These interactions are thought to be caused by an induction of the isoenzyme 3A4 of the cytochrome oxidase system, which metabolises a series of pharmacetical substances, and an induction of P-glycoprotein, which is responsible for an increase in excretion of drugs from the organism (e.g. via the mucosa of the gastrointestinal tract).

Both mechanisms appear to be involved in the particularly relevant interactions (cyclosporin, or protease inhibitors like indinavir). According to our current knowledge, various components are involved in the interactions (as also found for the antidepressant action). The fact that in cell culture experiments, hyperforin causes relatively pronounced induction of a promoter which is responsible for the expression of cytochrome 3A4 [40], has led in several authors to speculate the exclusive role for possible drug interactions under St. John’s wort therapy to hyperforin. According to present data, this is not justified, as other St. John’s wort components could also have an inductive or an inhibitory effect on cytochrome oxidases and on P-glycoprotein (e.g. biapigenin, flavonoids) [41,43,44]. This was also shown in a recently published investigation, in which a hyperforin-free extract induced both systems in man [44]. Furthermore, a new study published also demonstrates the special role of hypericin in the induction of P-glycoprotein [43].

14. Which interactions are relevant in practice?

The interaction of St. John’s wort extract with the immune suppressant cyclosporin is well documented with regard to the decrease in plasma level as well as the clinical consequences (risk of transplant rejection), so that here a clear contraindication for St. John’s wort is certainly the case. Furthermore, St. John’s wort extract should not be combined with indinavir and possibly not with other protease inhibitors used in HIV therapy, although these interactions (reduction in plasma level) have only been shown pharmacokinetically in volunteers and have not yet been shown to have clinical consequences. However, as precise adherence to the therapeutic conditions is particularly important in HIV therapy, caution is called for. A drug interaction which is confirmed both with regard to the pharmacokinetics as well as the pharmacodynamics, is the interaction with oral anticoagulants of the coumarin type. In this case, co-medication would certainly be possible if the coagulation parameters are regularly checked. This also applies to the pharmacokinetic interaction with digoxin, which so far has only been reported in volunteers, and is certainly no contraindication, and from some authors even considered to be clinically insignificant as the approximately 20% decrease in digoxin plasma levels is irrelevant in view of the high inter-individual variation in these values found in patients without Hypericum therapy.

An interaction of somewhat doubtful clinical relevance is the increase in antidepressant-related adverse events (SSRI) observed by several authors. Of more practical importance is the question of a possible interaction with oral contraceptives. In different countries, a number of cases of intracyclic menstrual bleeding under two-phase preparations with low oestrogen content have been observed. There are also isolated reports world-wide of unwanted pregnancies. Despite a very comprehensive presentation of this potential ADE in the specialist and popular press over the last 3 years, reports have not become more but rather less frequent over the past years. As spontaneous intracyclic menstrual bleeding occurs relatively frequently, particularly with the two-phase preparations with low oestrogen content, and unwanted pregnancies may also occur in isolated cases even when the pill is used correctly (and more often with incorrect use), the relevance of this interaction is probably much lower than originally thought. Nevertheless, it has recently been included in the product information sheets for the medical profession and for patients, as we cannot completely exclude the possibility of such interactions on the basis of the preclinical data. Consequently, during treatment with St. John’s wort extracts, patients should use additional contraceptive protection on critical days.

Despite these, in some cases confirmed, drug interactions, St. John’s wort extract must still be considered to be an antidepressant with superior tolerability, whereby this conclusion is based not only on clinical trials but also on post-marketing surveillance studies and pharmacovigilance systems which cover many million days of treatment. This does not alter the fact that in individual cases clinically relevant interactions with other drugs have been observed, which must be taken into account when using St. John’s wort extracts.

15. Assessment of St. John’s wort as an antidepressant

Today, the pharmacological action and therapeutic efficacy of St. John’s wort extract as an antidepressant must be considered as confirmed, despite two negative American studies mentioned. Within the wide range of components in St. John’s wort extract, hyperforin plays an important, if not an outstanding role.

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