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Current studies on the method of action and clinical efficacy of St. John's wort

Pal, sandar , Lewis

Department of Pharmacological Research

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Abstract

In several nations, preparations made from St. John's wort extracts are used to treat depression as a recognized substitute for behavioral therapy or synthetic antidepressants. As a result, the therapeutic application of St. John's wort extracts goes far beyond the conventional realm of herbal therapy. A summary of the state of preclinical and clinical research is provided. The neuronal absorption of gamma-aminobutyric acid (GABA), L-glutamate, noradrenaline, dopamine, and serotonin is all clearly inhibited by St. John's wort extract. No other antidepressant exhibits an inhibitory profile that is roughly as extensive. Numerous effects in several behavioral pharmacology models of antidepressant efficacy could also be shown for St. John's wort extract, in good agreement with the effects in various biochemical models of antidepressant action. The aforementioned neurotransmitter systems in the brain are likewise altered by comparable dosages of John's wort. Only hyperforin and its structural analogue adhyperforin, among all the constituents of St. John's wort, prevent the neurotransmitters under investigation from being reabsorbed. Nevertheless, hyperforin influences the sodium gradient, which subsequently results in an inhibition of uptake, rather than acting as a competitive inhibitor at the transmitter binding sites of the transporter proteins. Only the pure material hyperforin has been shown to exhibit the wide range of action typical of St. John's wort extracts. Even though an American study recently questioned the therapeutic efficacy of St. John's wort extracts, several excellent clinical trials conducted over the past year have confirmed the extracts' effectiveness and tolerability in moderate depressive disorders. Every study has attested to St. John's wort extract's excellent tolerance and extremely low incidence of side effects. However, St. John's wort extract has been linked to a number of medication interactions, some of which are clinically significant. In conclusion, numerous scientific studies attest to the pharmacological activity and therapeutic usefulness of St. John's wort extract as an antidepressant. Hyperforin has a significant, if not exceptional, significance among the several constituents in St. John's wort extract.

Keywords: hyperforin; pharmacological characteristics; antidepressant effectiveness; St. John's wort; side effect profile

Introduction

In several nations, preparations made from St. John's wort extracts are now often used to treat depression. They are a recognized substitute for behavioral therapy or synthetic antidepressants, especially for mild to moderate disorders [1–6]. Therefore, St. John's wort extract preparations are used not only for a common and potentially fatal disease (risk of suicide), but also for patients who suffer greatly and for a disorder that is very costly for our insurance system (medical consultations, medication, days off work, sick leave). As a result, the therapeutic application of St. John's wort extracts goes far beyond the conventional realm of herbal therapy.

Given this, it seems entirely reasonable to mandate that the use of St. John's wort preparations adhere to the standards of rational drug therapy, which are established by the legal authorities in terms of activity, efficacy, and safety. The current communication provides a summary of the current situation.

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

Although numerous molecular routes are implicated, it is now recognized that nearly all antidepressants affect the synaptic connection of the neurotransmitters serotonin and noradrenaline in the central nervous system. Most antidepressants increase noradrenaline and serotonin availability at the corresponding synapses, at least initially (Fig. 1).

The suppression of the intra- and extraneuronal enzyme monoamine oxidase (MAO), a mechanism that the MAO inhibitors take advantage of, is one potential mode of action. This slows down the degradation of both neurotransmitters and increases their concentration at the contact sites.

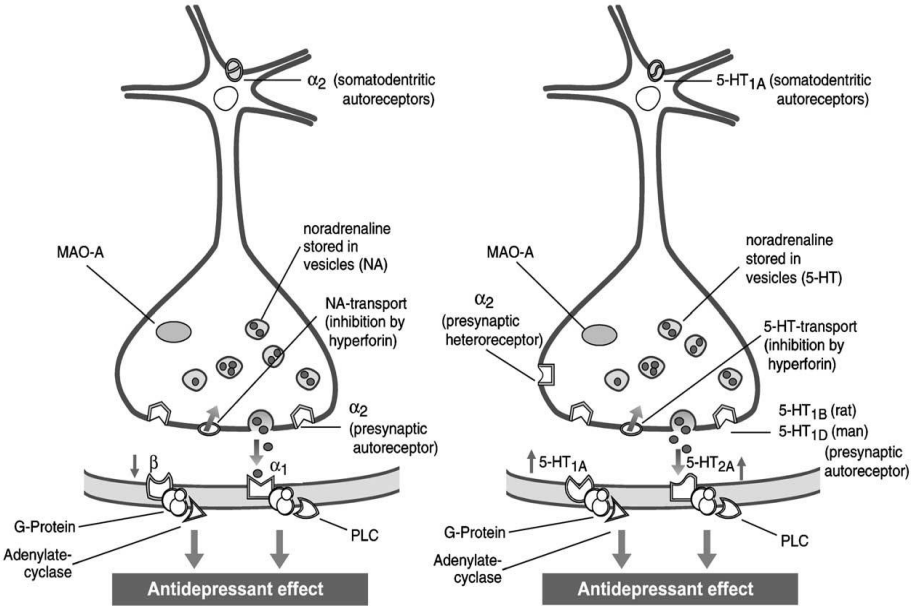

Fig. 1. The biochemical mechanism of action of St. John's wort extract exhibits similarities to that of other antidepressants. Many synthetic antidepressants lead to an increase in concentration of the two neurotransmitters noradrenaline and serotonin in the synapses (contact sites between nerve cells) 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 α_2-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 β-, 5-HT_{1A}- and 5-HT_{2A}-receptors (see arrows).

grew (Fig. 1). Our research was unable to validate previous studies that assumed St. John's wort extract had an inhibitory effect on the monoamine oxidase A enzyme (Fig. 1) and regarded the extract as a herbal MAO inhibitor [7].Although it applies to practically all antidepressants, both new and old, the most significant molecular mechanism of antidepressant efficacy is related to the traditional tricyclic antidepressants (TCA). The transport proteins that return neurotransmitters released into the synapse to the pre-synaptic portion of the synaptic contact are inhibited by TCAs (Fig. 1). The similar effect is produced by selective serotonin reuptake inhibitors, however they only work on serotonin transporters and not noradrenaline transporters.The nerve cells receiving the transmitter signal undergo adaptive changes in receptor shape, most likely due to the rising concentrations of both neurotransmitters in the synaptic gap (Fig. 1). As indicated by arrows in Fig. 1,

significant examples of these adaptive alterations are the decrease in β-receptor density in the noradrenergic synapse, the increase in 5-HT1A-receptor density in the serotoninergic synapse, or the decrease in 5-HT2A-receptor density. The gradually evolving antidepressant is correlated with the adaptive alterations' time cycle. These alterations are thought to be a significant part of the overall mechanism of antidepressant action, given the pressant effectiveness of all antidepressants (2–3 weeks).

2. St. John's wort extract has a broad spectrum of action

With a mean inhibitory dosage of 2 µg/ml, St. John's wort extract clearly inhibits the synaptosomal absorption of more than only serotonin (Table 1). We discovered similar inhibitory effects on the synaptosomal absorption of noradrenaline, dopamine, gamma-aminobutyric acid (GABA), and L-glutamate [8] (Table 1), which surprised us and stands in stark contrast to the features of all other antidepressants. According to the comparison data (Table 1), St. John's wort inhibits all systems with almost the same affinity, demonstrating a wider breadth of action than any known conventional antidepressant. The remaining antidepressants either exhibit overlapping inhibitory effects on a maximum of two of the investigated systems or are solely unique to one system. No other antidepressant that we are aware of exhibits roughly equivalent inhibitory effect on all five neurotransmitters' synaptosomal absorption.

Table 1
Mean inhibitory concentration (IC_{50}) of several antidepressants, hyperforin and of a St. John's wort extract on the synaptosomal uptake of various neurotransmitters

Substance	Serotonin uptake	Dopamine uptake	Noradrenaline uptake	GABA uptake	L-Glutamate uptake
IC_{50} (nmol/l)					
Imipramine	21	>1000	21	>1000	>1000
Clomipramine	1	>1000	14	>1000	>1000
Desipramine	207	>1000	3	>1000	>1000
Citalopram	1	>1000	>1000	>1000	>1000
Hyperforin	205	102	80	184	143
IC_{50} (µg/ml)					
St. John's wort extract	2[a]	1	5	1	11

Imipramine, clomipramine and desipramine are tricyclic antidepressants, citalopram is a substance belonging to the group of selective serotonin re-uptake inhibitors (SSRI). Lower numbers represent lower inhibitory concentrations and thus a higher pharmacological efficacy. Values are published findings from our laboratory [7,8,15].

[a] About 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])

Forced swimming (Porsolt's) test	Tail suspension test
Learned helplessness test	Reserpine test
Water wheel test	
Aggressiveness in socially isolated mice	Escape deficit model
Mild chronic stress	

3. Influence on neurotransmission in vivo

The fact that several authors discovered alterations in the central concentrations of the three neurotransmitters—noradrenaline, serotonin, and dopamine or their metabolites—in the central nervous systems of experimental animals following acute or long-term treatment is especially important for comprehending St. John's wort extract as an antidepressant. Regarding synthetic antidepressants, the results are inconsistent; however, distinct effects are noted based on the dosage, length of treatment, and brain region under investigation [9–12]. These results generally corroborate that the aforementioned neurotransmitter systems in the brain are altered in vivo by doses of St. John's wort (see Table 2) that are active in behavioral

tests. This establishes a connection between biochemical in vitro studies and in vivo alterations typical of antidepressants in the brain of experimental animals, as do the results on adaptive changes in receptor density provided in the next chapter.

4. Effects on the density of β- and 5-HT$_2$-receptors

By demonstrating that rats treated subchronically with imipramine or St. John's wort extract showed a significant decrease in β-receptor density, we could also validate an impact on noradrenergic and serotoninergic pathways in vivo. sity in the frontal cortex [7]. Recently, a β-specific radioligand (3H-CGP 1277) was used to confirm the results obtained with the rater less selective ligand 3H-DHA [13]. The 5-HT2-receptors in the frontal cortex could likewise be significantly down-regulated in rats given imipramine under otherwise equivalent settings [7]. However, the frontal cortex's 5-HT2-receptor density did not diminish as a result of the same treatment with St. John's wort extract; instead, the number of 5-HT2-receptors significantly increased [7]. Antidepressants often do not exhibit this tendency, although electroconvulsive therapy—also known as the "Ultima Ratio" in the treatment of depression—has been shown to be effective when nothing else. Thus, the pharmacological effects of St. John's wort extract on central noradrenergic and serotoninergic synapses are comparable to those of other antidepressants or antidepressant treatments (Fig. 1).

5. Behavioural pharmacology studies

Numerous working groups have shown that St. John's wort extract has numerous effects in several behavioral pharmacology models of antidepressant efficacy, which are in good accord with the effects in various biochemical models of antidepressant activity. These models included the reversal of a number of reserpine-induced behavior patterns, the removal of the immobilization time in the Por-solt test, and the reversal of helpless behavior in the learned helplessness model (Table 2). The fact that St. John's wort extract has demonstrated effectiveness in a number of behavioral pharmacology models, all of which are somewhat suggestive of an antidepressant action in humans, is quite significant. However, because false positive and false negative compounds recur, none of these models by themselves are adequately representative.Unfortunately, this also applies to the immobilization test (Porsolt test), which is frequently employed because to its relative ease of use. act. Originally, this test was designed for temporary use. For example, St. John's wort extract and tricyclic antidepressants are effective in certain situations. But the most popular antidepressants available today in the class of selective serotonin reuptake inhibitors (SSRIs) are not. The effectiveness of the SSRI can only be demonstrated in this model with a longer treatment duration (e.g., the 9 days routinely employed by us), and the benefits of St. John's wort extract become much more noticeable [14]. Preclinical research can only provide a reasonable estimate of the therapeutic efficacy in patients when many experimental models are employed. For extracts from St. John's wort, this is accurate.

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

Hypericin, a component crucial to the phototoxic action, was initially linked to the significant MAO-A inhibiting effect of St. John's wort extract, which was later never verified. Similarly, hypericin did not exhibit MAO inhibition [7]. Additionally, pure hypericin was ineffective in our studies on the synaptosomal absorption of serotonin, noradrenaline, dopamine, and GABA [15]. However, the nitrogen-free phloroglucinol derivative hyperforin (quantitatively also the most significant single constituent with 2–5%) could be identified as the active ingredient crucial for the synaptosomal uptake inhibition of all five transmitter chemicals (Table 1) [8,16]. We recently had the chance to examine almost all of the pertinent components of St. John's wort extract as individual compounds in relation to their role as reuptake inhibitors [15]. These results demonstrate unequivocally that only hyperforin and its structural equivalent, adhyperforin (methylated hyperforin), limit the reuptake of the neurotransmitters under investigation. A Danish team also confirmed this

[17]. Additionally, our research revealed that the oligomeric procyanidine fraction [15] can clearly account for the modest in vitro reuptake inhibition observed for hyperforin-free St. John's wort extracts [13].
Although the exact mechanism by which procyanidine produces this effect is unknown, it is highly improbable that these molecules contribute to the antidepressant effect due to their high hydrophilicity, as they most likely cannot penetrate the blood–brain barrier. Behavioral pharmacology studies have verified this, showing no impact of the procyanidine fraction in the immobility test [18].

7. Molecular mechanism of action of hyperforin

Exciting new details about hyperforin's molecular mode of action have also just surfaced. There is no competitive inhibitory effect of hyperforin at the transmitter binding sites of the transporter proteins, similar to all other antidepressants [17, 19–23], but exhibits a completely different mode of action. The sodium gradient between the high external and low intracellular sodium concentrations is what propels all of the high-affinity neuronal neurotransmitter transport mechanisms described. This sodium gradient drives all transport proteins in a way that essentially forces the neurotransmitter into the cell by co-binding sodium ions. We could demonstrate that hyperforin inhibits absorption by lowering the sodium gradient through the activation of an as-yet-unidentified sodium conductivity mechanism [20,21]. The peculiar discovery that hyperforin inhibits the absorption of many neurotransmitters to almost the same degree [8] is also explained by the sodium gradient's significance for all these transmitter uptake processes. Furthermore, biochemical alterations that confirm in vivo effects on the neurotransmitter systems typical of antidepressants (e.g., β down-regulation or changes in transmitter or metabolite concentrations) were observed in the brain following acute or repeated administration of hyperforin in experimental animals [10,11,16].

8. Effects of hyperforin on behaviour

Several publications have also shown the dominating role of hyperforin in behavioral pharmacology trials (Table 3). According to our preliminary results, hyperforin played a major role in determining the action of St. John's wort extract in the immobilization and learned helpless paradigms [8]. We and numerous other organizations have obtained similar results for numerous additional behavioral models [23–26]. Under our conditions, activity can still be detected in the Porsolt test if hyperforin is eliminated from the extract, indicating the presence of additional active substances; however, the hyperforin-free extract's action was less pronounced [14]. Hyperforin-free extract is ineffective in other models, such as the reserpine test, a traditional model, especially for tricyclic antidepressants [14]. In several other analogous experimental settings, hyperforin-free extracts have not yet demonstrated a sufficient effect (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])

Learned helplessness
Porsolt test (under certain conditions)
Elevated plus maze (anxiolysis) (hypericin is ineffective) Passive avoidance learning (cognition)
Avoidance deficit model
Increase in extracellular serotonin and dopamine concentrations in micro-dialysis experiment
Release of growth hormone

Table 4
Pharmacological models in which hyperforin-free St. John's wort extracts were not effective [11,14,24,25,26]

Reserpine test (depression) Scopolamine test (depression)
Passive avoidance learning (cognition)
Increase in extracellular serotonin, GABA and L-glutamate concentrations

Table 5
Pharmacological characteristics beyond depression, which so far have only been demonstrated for hyperforin (after [24,25,48,49])

1. Anxiolysis (elevated plus maze)
2. Cognition improvement (passive avoidance learning)
3. Increased APP processing (stimulation of α-secretase)

Moreover, only hyperforin has demonstrated pharmacological effectiveness in scenarios outside the real antidepressant activity thus far (Table 5). It is important to discuss anxiolytic effects in particular. Once more, these serve as a link to contemporary SSRI antidepressants, whose effectiveness in treating various anxiety states or symptoms has been thoroughly established. In the passive avoidance learning model, St. John's wort extracts with hyperforin and pure hyperforin (but not extracts without hyperforin) are also beneficial. Rather than an antidepressant impact, this suggests an enhancement in learning and memory ability. Additionally, we recently reported that hyperforin affects the metabolism of the amyloid precursor protein molecule, which may be a sign of α-secretase activity (Table 5). Only the pure compound hyperforin has been shown to exhibit the wide range of action that characterizes St. John's wort extracts. Therefore, hyperforin must be regarded as the most well-documented active ingredient in St. John's wort extract at the moment. While hyperforin-free extracts work well in the Porsolt model, for example, they are ineffective or insufficiently effective in several other pertinent models.

9. Other active ingredients

Even though hyperforin is the primary active constituent in St. John's wort extract, it is now evident that other compounds work well in several pharmacological models. But compared to hyperforin, these compounds' pharmacological characteristics are by no means as well-documented. Recently, hypericin itself was found to have an effect in the Porsolt test [18]. However, this has not been discovered by other writers [14]and was not discovered by the same authors in previous publications. Rats under hypericin showed intriguing endocrinological alterations after an 8-week dosing interval. However, given the incredibly lengthy administration interval required, the significance of this for the antidepressant effect must be regarded as dubious [27]. The importance of hypericin, which was previously thought to thought to be the primary active component, is still up for debate, especially as it doesn't seem to permeate the blood-brain barrier [28]. On the other hand, results for several flavonoids, particularly hyperoside, show action in the immobilization test at tolerable dosages and are more consistent [14,29]. our also applies to I3, II8-biapigenin, which may have a considerably weaker effect at larger doses but was effective in our model at even lower concentrations [14]. There is no information available regarding these compounds' biological mechanism of action or how they function in different models. However, Philippu was able to demonstrate that, in contrast to St. John's wort extract containing hyperforin and hyperforin itself, hyperforin-free St. John's wort extract can also raise the extraneuronal concentrations of dopamine and norepinephrine while decreasing the serotonin concentration [11]. It's noteworthy to note that, unlike I3, II8-biapigenin, hyper-oside and other flavonoids are not unique to St. John's wort; rather, they may be found in comparatively high amounts in a variety of other officinal plants and even vegetables. Naturally, the question is whether a hyperforin-free extract works as an antidepressant as well. Only the hyperforin-rich extract outperformed the placebo in a research by Laakman et al. [30] that examined two St. John's wort extracts with either a high or low hyperforin content in depressed patients. These results contrast with a separate St. John's wort extract that was low in hyperforin and shown notable benefits over a placebo in a clinical study [21].

The placebo group in this study did not significantly improve, in contrast to hundreds of other antidepressant studies; however, at the end of the study, the group's arithmetic performance was marginally worse [31]. The validity of this study should at the very least be discussed because this is such an unexpected finding. Low hyperforin St. John's wort extract has demonstrated similar therapeutic results to imipramine or fluoxetine in

two earlier investigations [32, 33]. However, these studies lacked placebo groups, which is now a standard condition for comparative studies. As a result, no definitive conclusions can be drawn from those investigations. According to the available data, hyperforin-low St. John's wort extracts may thus also exhibit some therapeutic impact, albeit one that is less pronounced than that of hyperforin-rich extracts. Additionally, it is believed that compounds with multiple modes of action have advantages over pure serotonin or noradrenaline reuptake inhibitors when it comes to synthetic antidepressants [34].

10. Clinical efficacy

Although St. John's wort extracts were initially used for therapeutic purposes, their widespread adoption, as seen in Germany and a few other nations today, can only be explained by the fact that several excellent clinical studies have been conducted in recent years that confirm St. John's wort extracts' effectiveness and tolerability in treating mild depression (for reviews [1–6]). An American study has questioned the treatment efficacy [35]. Based on two more recent clinical investigations, it is important to summarize the benefits and drawbacks of using St. John's wort extract to treat depressive disorders.

11. A comparison of two most recent clinical studies

In the widely cited "negative" American trial [35], patients with an initial Hamilton Depression Scale (HAMD) score of at least 20 were included in a multicenter, randomized, double-blind, placebo-controlled study. The double-blind treatment research lasted eight weeks after a single-blind placebo run-in phase. A number of other self- and third-party assessment scales were also examined, although the HAMD was the main evaluation criterion.Since there was no discernible difference between the placebo and St. John's wort curves, the main conclusion of this study was that there was no difference in the time course of the HAMD primary target criterion over the period of eight weeks. This also held true for most of the other scales that were examined. Nonetheless, a numerical advantage of St. John's wort extract over placebo was discovered, but not statistically significant, when the proportionate distribution of responders (50% or greater improvement at end point) is taken into account. The placebo response (14%) was remarkably low overall. In contrast, nearly three times as many remissions were seen under St. John's wort extract as under a placebo when it came to the rate of remission (HAMD values <7 at the end of the research, i.e., symptom-free patients). There was a statistically significant difference. Although the primary target criterion of this study is HAMD, there is still some data supporting the effectiveness of St. John's wort. However, the study stands in stark contrast to nearly every previous clinical trial.as the research that is covered below [37].

This study by Shelton et al. [35] comprised extremely sick patients with a mean duration of depressive illness of around ten years. The average duration of the acute depression phase treated with St. John's wort or a placebo in the trial was two years, which is likewise very long for a study of this kind. Additionally, the melancholy subtype, which is also suggestive of severe depression, was identified in more than 40% of the patients. Despite this, the patients' average HAMD score at trial enrollment was only 22, which seems to be low.The therapeutic use and registered indications of St. John's wort extracts in Germany, which only treat mild to moderate depression, contrast sharply with the inclusion of patients with severe and chronic depression. For the patients in the Shelton trial, many doctors who voluntarily and regularly administer St. John's wort extracts would not have done so.

12. Tolerability and interactions

The two clinical trials discussed in this review attested to St. John's wort extract's excellent tolerability and extremely low incidence of side effects. As stated in Section 1 [1–6], this highlights once more the indisputable

benefit of St. John's wort in the outpatient treatment of depressive disorders. The evaluation of St. John's wort extract as a largely trouble-free treatment had to be updated recently in a few areas due to the discovery of certain medication interactions with St. John's wort extracts, some of which include clinically significant. Since this subject has been covered in several recent papers [39–41,43,44], just a brief synopsis and evaluation will be provided here. There have been reports of a decrease in the plasma levels of several different drugs when co-medicated with St. John's wort, though not all cases have shown clinical effects. The cytochrome oxidase system's isoenzyme 3A4, which metabolizes a number of pharmaceutical substances, and P-glycoprotein, which increases drug excretion from the body (e.g. via the mucosa of the gastrointestinal tract), are thought to be the causes of these interactions. Both mechanisms appear to be involved in the particularly relevant interactions (cyclosporin, or protease inhibitors like indinavir). Our current understanding indicates that the interactions entail a number of different components (as was observed for the antidepressant activity). Because hyperforin causes a relatively strong induction of a promoter that is responsible for the expression of cytochrome 3A4 in cell culture experiments [40], some authors have speculated that hyperforin may play an exclusive role in potential drug interactions under St. John's wort therapy. 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 demonstrated in a recently published study where both systems were stimulated in humans using a hyperforin-fee extract [44]. Additionally, a recent study shows that hypericin has a unique role in P-glycoprotein induction [43].

14.Which interactions are relevant in practice?

There is undoubtedly a strong contraindication for St. John's wort in this situation due to the well-documented interaction between the immune suppressant cyclosporin and St. John's wort extract, including the reduction in plasma level and the clinical consequences (risk of transplant rejection). Additionally, even though these interactions (a decrease in plasma level) have only been demonstrated pharmacokinetically in volunteers and have not yet been demonstrated to have clinical implications, St. John's wort extract should not be combined with indinavir and possibly not with other protease inhibitors used in HIV therapy. However, vigilance is required because HIV therapy requires exact adherence to the therapeutic conditions. The interaction with oral anticoagulants of the coumarin type is a pharmacological interaction that has been verified in terms of both pharmacokinetics and pharmacodynamics. If the coagulation parameters are routinely monitored, co-medication would undoubtedly be feasible in this situation. This also holds true for the pharmacokinetic interaction with digoxin, which has only been documented in volunteers thus far. It is undoubtedly not a contraindication and, according to some authors, is even clinically minor given the about 20% drop in digoxin plasma levels is unimportant given the significant inter-individual variance in these values observed in patients who do not get Hypericum medication. The rise in antidepressant-related adverse events (SSRI) reported by multiple authors is an interaction of questionable therapeutic significance. The issue of potential interactions with oral contraceptives is more practically significant. Numerous instances of intracyclic menstrual hemorrhage under two-phase preparations with low estrogen levels have been reported in various nations. Additionally, there are isolated accounts of unintended pregnancies all across the world. Reports have not increased over the past three years, but rather decreased, despite a very thorough presentation of this potential ADE in the specialized and public press. The relevance of this interaction is probably much lower than initially believed because spontaneous intracyclic menstrual bleeding happens rather frequently, especially 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 frequently with incorrect use). However, as we cannot totally rule out the possibility of such interactions based on preclinical research, it has recently been included to the product information sheets for patients and the medical community. As a result, patients should take extra contraceptive protection on crucial days while taking St. John's wort extracts. St. John's wort extract

must still be regarded as an antidepressant with superior tolerability despite these, in some cases, confirmed drug interactions. This conclusion is based not only on clinical trials but also on post-marketing surveillance studies and pharmacovigilance systems that cover millions of treatment days. This does not change the fact that there have been isolated instances of clinically significant interactions with other medications, which should be considered while using extracts from St. John's wort.

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

Despite the two reported unfavorable American investigations, the pharmacological action and therapeutic efficacy of St. John's wort extract as an antidepressant must now be regarded as proven. Hyperforin has a significant, if not exceptional, significance among the several constituents in St. John's wort extract.

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