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St. John's Wort – an Overview

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Key Words
Hypericum · St. John's wort · Depression · Interactions

Summary
This article aims to summarize the current state of knowledge on St. John's wort (*Hypericum perforatum* L.) which is one of the oldest and best investigated medicinal herbs. Dried alcoholic extracts are the most important preparations on the market although a variety of other preparations are available. Depressive disorders according to modern diagnostic standards are the best known and most widely investigated indication although the more traditional, broader indication of 'psycho-vegetative disorders, depressive disorders, anxiety and/or nervous agitation', including diagnoses such as somatoform disorders, might more adequately describe what Hypericum extracts are actually used for by many practitioners. The exact mechanisms of action are still unclear, but the available research clearly shows that various bioactive constituents contribute to the clinical effects reported, often in a synergistic manner. Hypericum extracts have consistently shown activity in pharmacological models related to antidepressant effects. Randomized clinical trials show that Hypericum extracts are more effective than placebo and similarly effective as standard antidepressants while having better tolerability in the acute treatment of major depressive episodes. The most important risk associated with Hypericum extracts are interactions with other drugs. Therefore, physicians need to be informed whether their patients take St. John's wort products. If the risk of interactions is adequately taken into account, high quality Hypericum extracts are an effective and safe tool in the hand of qualified health professionals in primary care.

Schlüsselwörter
Hypericum · Johanniskraut · Depression · Interaktionen

Zusammenfassung
Der vorliegende Artikel gibt einen Überblick über den aktuellen Wissensstand zu Johanniskraut (*Hypericum perforatum* L.), einer der ältesten und am besten untersuchten Arzneipflanzen. Auf dem Markt ist eine große Zahl unterschiedlicher Zubereitungen erhältlich, bei den wichtigsten Präparaten handelt es sich aber um alkoholische Extrakte aus getrockneten Pflanzen. Die am häufigsten untersuchte und diskutierte Indikation sind Depressionen entsprechend moderner diagnostischer Klassifikationen; der weiter gefasste traditionelle Indikationsbereich «psychovergetative Störungen, depressive Verstimmungszustände, Angst und/oder nervöse Unruhe», inklusive solcher Diagnosen wie der somatoformen Störung, dürfte jedoch der tatsächlichen Verwendung in der ärztlichen Praxis besser entsprechen. Die exakten Mechanismen der klinischen Wirkungen von Johanniskrautextrakten sind nicht vollständig aufgeklärt; es besteht jedoch weitgehend Konsens, dass verschiedene bioaktive Inhaltsstoffgruppen häufig synergistisch zusammenwirken, sodass der Gesamtextrakt und nicht Einzelsubstanzen als wirksames Prinzip angesehen werden muss. Die antidepressive Wirkung von Johanniskrautextrakten wurde in verschiedenen pharmakologischen Modellen nachgewiesen. Randomisierte klinische Studien belegen, dass Johanniskrautextrakte bei leichten bis mittelschweren Depressionen wirksamer als Placebo und ähnlich wirksam wie synthetische Antidepressiva bei besserer Verträglichkeit sind. Das relevanteste Risiko beim Einsatz von Johanniskrautpräparaten sind Interaktionen mit anderen Arzneimitteln. Daher müssen Ärzte über die Einnahme entsprechender Präparate informiert sein. Bei angemessener Beachtung des Interaktionsrisikos stellen Johanniskrautextrakte in den Händen von ausreichend informierten Ärzten eine wirksame und sichere Option im oben genannten Indikationsbereich dar.

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What Is St. John's Wort, How Is It Prepared, and What Is It Used for?

St. John's wort (*Hypericum perforatum* L.) is a yellow-flowering, perennial herb native to Europe, West Asia, and North Africa, which has been naturalized to North and South America as well as Australia [1]. The common name comes from its traditional flowering and harvesting on St. John's day, 24 June. The genus *Hypericum* belongs to the family *Clusiaceae* and contains approximately 370 species [2]. The word '*Hypericum*' comes from the Greek words hyper (above) and eikon (picture), indicating its use as a plant hanging over pictures of gods to keep the owner from evil powers [3]. The denotation '*perforatum*' refers to the presence of small oil glands in the leaves that look like perforations [3]. If the yellow petals are crushed, a dark-red oil emerges from these glands. St. John's wort is among the oldest medicinal herbs in Europe and was already used in antiquity and the Middle Ages [4, 5].

Based on this long history, a great variety of preparations is used. The flowering fresh plants or the dried aerial parts are typically used as basic material (*Hyperici herba*) [6, 7]. The quality of the raw plant material is fundamental for the preparation of products with a high and constant quality. External influences such as climate and the conditions and timing of harvesting and drying lead to variable quality of the raw material. Therefore, manufacturers typically mix plant material from cultivated and non-cultivated sources, different places, and years [7]. Important bioactive components are concentrated in buds, blossoms, and tips of twigs [8]. From fresh plant material homeopathic mother tinctures, pressed juices, or oils are prepared (fig. 1). The majority of phytopharmaceuticals used for depression treatment are dried extracts which have undergone a complex and highly sophisticated preparation process. Dried plant material is also used to prepare further oil products, fluid extracts, or teas. It is evident that depending on the manufacturing process the compounds contained in Hypericum preparations vary in quality and quantity.

As most research has been done on alcoholic extracts from dried *H. herba* we refer to this type of preparations if we talk about the term Hypericum extracts in the following.

Today, the primary indication of St. John's wort products is depression according to modern diagnostic criteria. The recent monograph of the European Scientific Cooperative on Phytotherapy (ESCOP) lists as therapeutic indications for hydroalcoholic extracts and tinctures 'episodes of mild depressive disorders or mild to moderate depressive episodes' according to ICD-10 (International Classification of Diseases 10th revision; F32.0, F32.1, F33.0, F33.1) [9]. However, the traditional use of such products is much broader. According to the monograph of the commission E at the former German Federal Institute of Health (Bundesgesundheitsamt) from 1984, extracts of *H. herba* can be used for 'psycho-vegetative disorders, depressive disorders, anxiety and/or nervous agitation' [6]. ICD-10 diagnoses reflecting the traditional use also include somatoform disorders (F45.0), neurasthenia (F48.0), and adjustment disorder (F43.2) [10].

Oil-based preparations can be used for 'dyspeptic complaints'. Furthermore, external applications of oil-based preparations are applied to treat injuries, myalgia, or minor burns [6].

However, beyond these usual indications a large variety of further indications has been described in different sources (cf. [10]).

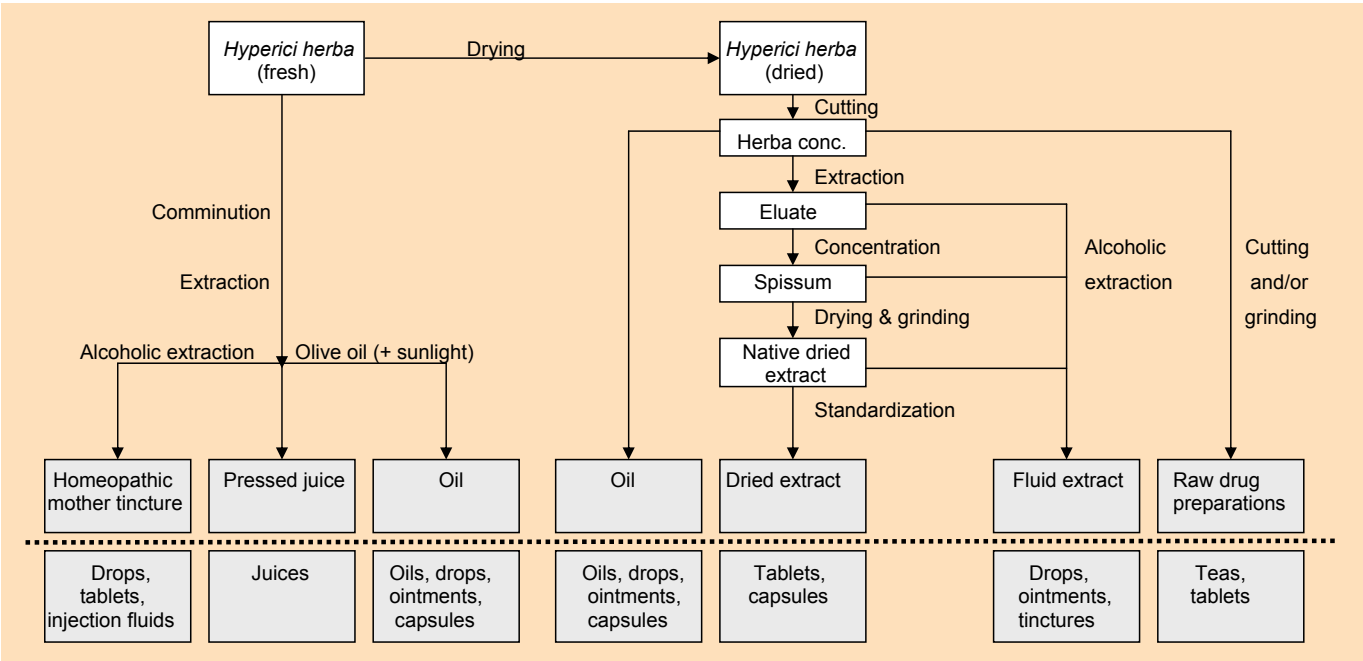

Fig. 1. Preparation of different kinds of Hypericum products (modified from Gaedcke [7]).

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Table 1. Important biologically active compounds found in St. John's wort *(Hypericum perforatum)* (modified from [7, 9, 13–15])

Component group	Examples	Plant parts	Action
Naphthodianthrones (lipophilic)	hypericin pseudohypericin	flowers, buds	antidepressant, antiviral, photosensitizing
Phloroglucinols (lipophilic)	hyperforin adhyperforin	flowers, buds	antidepressant, antibiotic
Flavonoids (lipophilic/hydrophilic)	quercetin hyperoside quercitrin isoquercitrin rutin	leaves stalk buds	antidepressant, antiphlogistic
Biflavonoids (lipohilic)	biapigenin	flowers	sedating, antiphlogistic
Procyanidins (hydrophilic)	procyanidin catechin epicatechin	aerial parts flowers, buds	antiphlogistic, antioxidant
Essential oils (lipophilic)	terpenes alcohols	flowers, leaves	
Amino acids (hydrophilic)	GABA	flowers, leaves	antidepressant
Phenylpropanes (hydrophilic)	caffeic acid chlorogenic acid	flowers, leaves	
Xanthons (lipophilic)	norathyriol	roots, flowers	antidepressant

Hypericum extracts are among the best characterized herbal medicines. More than 150 ingredients or groups of ingredients with a multiplicity of additive, synergistic, and partly also antagonistic effects have been identified so far [4, 5, 11–13]. Still, 30–50% of its compounds are as yet not structurally defined and some of these might well contribute to the clinical effects [13]. Table 1 lists important bioactive ingredients.

The most characteristic constituents of *H. perforatum* are naphtodianthrones (hypericin and pseudohypericin) and phloroglucinols (hyperforin and adhyperforin) [7, 9, 11–15]. Hypericins constitute the crimson pigments in the flowers and leaves. Depending on the developmental stage, the concentration of hypericins and pseudohypericins in crude drug material varies between 0.03 and 0.3%. Hypericins are responsible for the photosensitizing effect of Hypericum extracts and contribute to the antidepressant effects. Furthermore, antiviral effects have been observed [15]. Hyperforin and adhyperforin occur exclusively in the generative parts of St. John's wort, especially in the unripe fruits [13]. Hyperforin seems to have considerable antidepressant activity [16], but also seems to be mainly responsible for the interactions with other drugs [17]. Furthermore, extracts almost devoid of hyperforin also have been shown to have clinical efficacy [18, 19]. The hyperforin content in available extracts varies strongly from almost 0 to up to 6%. Here, the extraction solvent seems to play a major role. While the content of hypericins is similar if any alcoholic extraction solvent containing ≥50% ethanol or methanol is used, the content in hyperforin and adhyperforin varies strongly depending on the alcohol concentration [10].

Flavonoids are less characteristic for *H. perforatum* but still play an important role in its biological effects both in quantitative and in qualitative terms relating to biological effects. With 2–4%, flavonol glycosides represent the largest group of secondary metabolites in St. John's wort [13]. The most important compounds are rutin, hyperoside, isoquercetin, quercitrin, and in smaller amounts quercetin. Flavonoids seem to have antidepressant properties but definitively act as co-effectors by improving pharmaceutical properties of other ingredients such as hypericins [13]. The biflavonoids biapigenin and amentoflavone again are characteristic for *H. perforatum* and occur exclusively in the flowers. For these compounds, sedating and antiphlogistic effects have been reported [7]. Other important compounds include procyanidines, tannins, essential oils, amino acids, phenylpropanes, and xanthones [14].

How Does It Work?

By far the most pharmacological research has been done to investigate the antidepressant activity of St. John's wort extracts. Most currently known antidepressants inhibit the reuptake of monoamines (norepinephrine, serotonin, dopamine) from the synaptic gap into the neuron [16]. The inhibition of monoamine uptake forms the basis for the classic hypotheses on the pathophysiology of depression and the mechanism of action of antidepressant drugs, which are classified accordingly as monoamine oxidase (MAO) inhibitors, norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors (SSRIs).

Early in vitro research suggested that the inhibition of the MAO enzyme is the main antidepressant mechanism of Hypericum extracts. However, although several studies have

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Table 2. Packages (in thousands) of Hypericum preparations (excluding combinations) sold in Europe (any sales channel) in three time periods. Data kindly provided by IMS Health

	4/2005–3/2006	4/2006–3/2007	4/2007–3/2008
Germany	5,040	4,520	3,786
Russian Federation	2,092	2,299	2,198
Poland	1,576	1,524	1,577
France	423	473	528
Ukraine	485	515	434
Switzerland	285	263	257
Other European countries	904	842	804
Total	*10,805*	*10,437*	*9,583*

demonstrated that MAO inhibitors are present in St. John's wort extracts, their effective concentrations are too low to explain the clinical antidepressant effects [12]. There is good evidence from in vitro experiments that Hypericum extracts and, in particular, hyperforin and adhyperforin are potent but non-specific inhibitors of the synaptosomal reuptake of serotonin, noradrenaline, and dopamine [12, 16]. Hyperforin-free extracts are also able to inhibit reuptake systems in a weak to moderate manner which could be due to oligomeric procyanidins [20]. In vivo studies have shown that Hypericum extracts lead to a downregulation of β-adrenergic receptors and an upregulation of 5-HT_2 receptors [12].

Hypericum extracts have been shown active in typical animal models such as the forced swimming test, the learned helplessness paradigm, or the model of escape deficit [10, 12, 16] used to test the antidepressant effects of drugs. The draft report of the Committee on Herbal Medicinal Products (HMPC) at the European Medicines Agency (EMEA) further summarizes the pharmacological evidence regarding anxiolytic effects, addiction, and antibacterial and anti-inflammatory activity [10]. The available evidence gives high plausibility to the antidepressant effects of Hypericum extracts reported in clinical studies, but the discussion is still ongoing on which constituents are most relevant.

Which Preparations Are on the Market and How Widespread Is Their Use?

It is extremely difficult to achieve an overview of the St. John's wort products available in different countries and how frequently these products are used. In most countries, St. John's wort products are marketed as supplements. Within the European Community, St. John's wort products are available both as food supplements and as drugs (and among the drugs, both in the categories 'well-established use' and 'traditional use'). In the United States, St. John's wort is available as a dietary supplement and is therefore not subject to stringent drug regulations.

Regarding the year 2006, the author reviewed available lists for Hypericum products in Germany [21]. In the 'Red List', the directory of drugs licensed in Germany used by most practising physicians, 40 preparations from 28 pharmaceutical

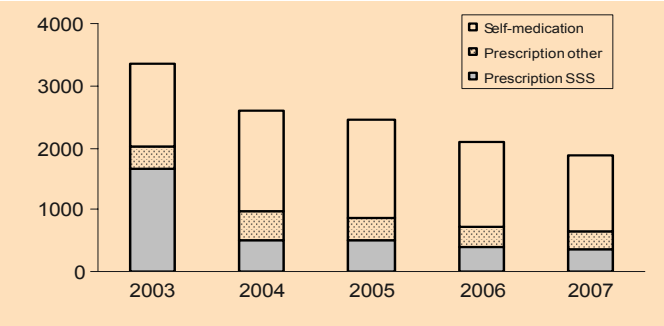

Fig. 2. Packages (in thousands) of Hypericum preparations sold in German pharmacies in 2003–2007. Data kindly provided by IMS Health. Prescription SSS = prescriptions from physicians reimbursed with statutory sickness fund system; prescription other = prescriptions from physicians reimbursed by private health insurance funds or not reimbursed.

companies were listed in the chapter on antidepressants. Most were dried extracts and available as capsules, tablets, or coated tablets. Daily extract dosages ranged from 80–1,700 mg but most often were between 500 and 1,200 mg (which seems a reasonable dose range for effective application). In most extracts, ethanol (50–80%) was used for extraction, in a minority methanol. Drug-extract ratios were typically in the range between 3:1 and 7:1. As specifications are identical in a number of preparations, it is likely that in fact several companies use the same extract for their product. Taking into account that also other directories include preparations which can be sold outside of pharmacies resulted in about 60 additional products [21]. For many products sold outside pharmacies in Germany, the concentration and daily dosages of relevant constituents are far below those assumed to be necessary for relevant clinical effects [22]. Products only marketed by pharmacies in general have adequate quality but variations of composition occur from batch to batch [23].

Market data are not easily accessible outside the pharmaceutical industry. Mediated by a manufacturer, the author obtained some market data from a company specialized in this area (IMS Health, *www.imshealth.de/de/startseite*). According to these data, >9.5 million packages of St. John's wort were sold in Europe between April 2007 and March 2008 (table 2). The most important markets are Germany (about 3.8 million packages sold), the Russian Federation (2.2 millions) and Poland (1.6 millions); together these three countries cover 79%

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Table 3. Summary of the findings from meta-analyses of randomized controlled trials of Hypericum extracts in patients suffering from depressive disorders [39, 42]

	Trials, n	Patients, n	Random effects, RR, 95% CI	I^2, %
Trials not limited to major depression				
All placebo-controlled trials	12	823	2.60 (1.69; 3.98)	76
– Less precise trials	6	332	5.33 (2.96; 9.59)	17
– More precise trials	6	491	1.78 (1.24; 2.55)	68
Trials limited to major depression				
All placebo-controlled trials	18	3,064	1.48 (1.23; 1.77)	75
– Less precise trials	9	1,020	1.87 (1.22; 2.87)	79
– More precise trials	9	2,044	1.28 (1.10; 1.49)	75
– All trials from German-speaking countries	11	1,770	1.78 (1.42; 2.25)	75
– All trials from other countries	7	1,294	1.07 (0.88; 1.31)	45
All trials vs. standard antidepressants	17	2,810	1.01 (0.93; 1.12)	17
– All trials vs. older antidepressants	5	1,016	1.02 (0.90; 1.15)	0
– All trials vs. SSRIs	12	1,794	1.00 (0.90; 1.12)	29
– All trials from German-speaking countries	9	1,952	1.04 (0.96; 1.13)	8
– All trials from other countries	8	817	0.90 (0.76; 1.06)	12

RR = Relative risk (proportion responder Hypericum group / proportion responders control group); CI = confidence interval; I^2 = a measure for the heterogeneity of study results (values between 25 and 50% indicate moderate heterogeneity, >50% substantial heterogeneity); SSRIs = selective serotonin reuptake inhibitors.

of all sales in Europe. Sales in Germany have been decreasing in recent years (fig. 2). In 2003, rules for prescription were changed, excluding almost all non-prescription drugs, including (with few exceptions) St. John's wort products, from reimbursement within the statutory sickness fund system (covering about 90% of the German population). As a consequence, prescription rates of St. John's wort extracts dropped sharply while figures for self-medication and prescriptions outside the statutory system remained stable. In the same time period, there was a considerable increase in prescriptions of SSRIs which are classified as prescription drugs [24].

Regarding the United States, the author has only rough sales data. In 2007, St. John's wort products ranked 10th among the top-selling herbal dietary supplements, with a total turnover of 8.1 million USD. Compared to 2006, this was a decrease by 5.6% [25].

What Is the Evidence Base Regarding Depression? Data on Efficacy and Effectiveness

More than 50 randomized controlled trials and more than 15 larger observational studies have investigated the effectiveness of Hypericum extracts in the acute treatment of depressive disorders. The first trial became available in 1979 [26], and until the mid 1990s about 25 trials were published which were exclusively performed in German-speaking countries. This evidence was summarized in a number of systematic reviews [27–32]. These early trials showed mostly clear-cut effects over placebo controls (table 3, upper part). Trials comparing Hypericum extracts with standard antidepressants such as imipramine, amitriptyline, or maprotiline were relatively rare and difficult to interpret due to a lack of statistical power or a low dosage of antidepressants. Diagnoses in many of these studies were made according to ICD-9 and often included neurotic depression or adjustment disorder (e.g. [33–36]). Some psychiatrists commented that the diagnoses of patients in these older studies, according to new classification systems such as ICD-10 or DSM-IV (Diagnostic and Statistical Manual for Mental Disorders, 4th edition), probably more closely matched categories such as adjustment disorder with depressed mood or acute stress disorder [37]. The studies were also criticized for diagnostic heterogeneity and lack of research experience among study physicians [38]. However, the participants in these early studies probably matched quite well the patient population actually treated with Hypericum extracts in routine practice in Germany, Austria, and Switzerland. Most of these early studies were not published in peer-reviewed journals and reported in suboptimal manner according to today's standards. Response in placebo groups was often low [39, 40]. Still, on a formal methodological level most trials seem straightforward and sources of bias are difficult to detect. However, the size of differences between placebo and Hypericum groups were much smaller in more precise (larger) trials than in less precise (smaller) trials which often reported extremely positive findings (table 3) [39, 40]. This is typically interpreted as a strong indicator of bias [41].

In order to better meet the modern requirements for depression research, more recent randomized trials were restricted to patients meeting the DSM-IV criteria for major depression or the corresponding diagnosis of a depressive episode according to ICD-10. The current version of the Cochrane systematic review of Hypericum extracts for major depression [42] includes a total of 29 double-blind, randomized trials in about 5,500 participants. The main outcome measure regarding effectiveness in this review was the proportion of patients responding

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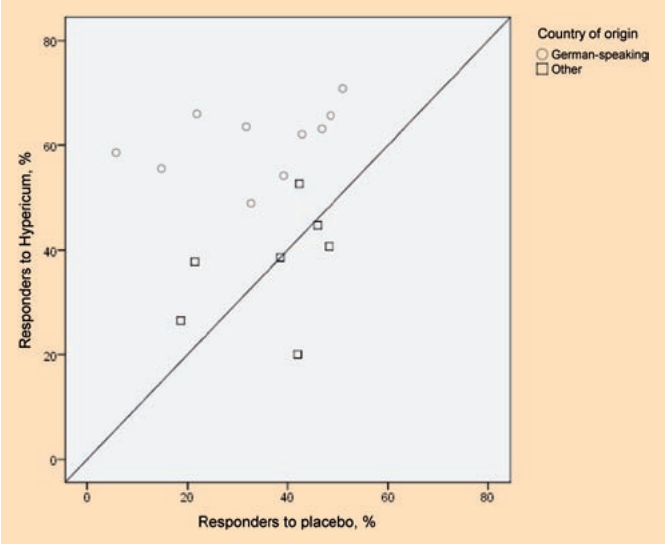

Fig. 3. Percentage of patients responding to Hypericum treatment and to placebo treatment in placebo-controlled trials.

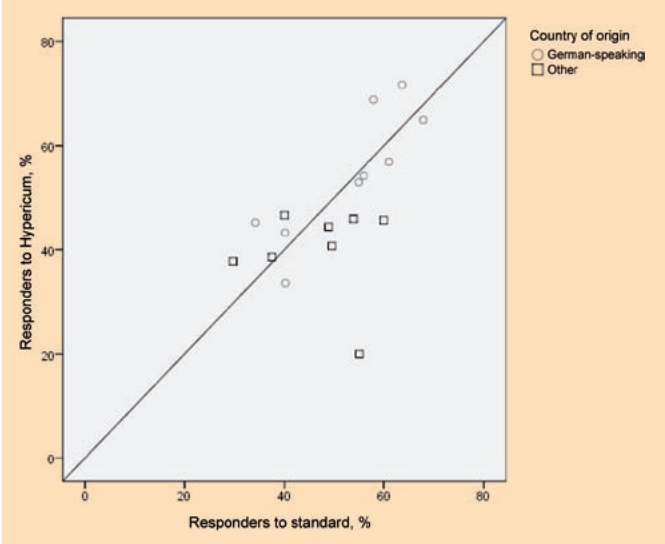

Fig. 4. Percentage of patients responding to Hypericum treatment and to standard antidepressant treatment.

in the Hypericum group divided by the proportion responding in the control group. This measure corresponds to a relative risk, but numbers >1 indicate superiority of Hypericum while those <1 indicate superiority of the control intervention.

Overall, the available evidence indicates that the tested Hypericum extracts are superior to placebo and similarly effective as standard antidepressants for the treatment of acute depression. The relative risk (ratio of the proportion of responders) compared to placebo was 1.48 (95% confidence interval (CI) 1.23–1.77) and compared to standard antidepressants 1.01 (0.93–1.12; table 3). Another independently performed recent meta-analysis also found similar effects of Hypericum extracts and SSRIs [43].

However, particularly among the placebo-controlled trials, the findings of single trials vary strongly [42]. This variation or heterogeneity cannot be explained by chance alone and is more pronounced than in trials of antidepressants (e.g. [44]). From the viewpoint of herbal medicine, variable extract quality or dosage would seem a logical explanation. But even if trials with identical preparations were analyzed separately, there was marked heterogeneity in most subgroup analyses [21, 42]. Based on meta-regression analyses in the Cochrane review, the heterogeneity seems to be associated with at least three factors [42]. As in trials which were not limited to patients with major depression, more precise trials showed on average smaller (but still significant) effects over placebo than less precise trials. There was also a trend that trials in patients with more severe symptoms yielded slightly less positive findings. The most interesting and puzzling result, however, was that trials from German-speaking countries had significantly more positive results than trials from other countries (fig. 3). While response rates in placebo groups are broadly similar, response rates in Hypericum groups are much higher in trials from German-speaking countries. If the seven trials from other countries are pooled separately, the difference between Hypericum extracts and placebo are not statistically significant. Comparisons between Hypericum extracts and standard antidepressants showed little heterogeneity, but again there are some hints of a country effect (cf. fig. 4 and table 3).

The reasons for the 'country effect' are unclear. One potential explanation is that patients in trials from German-speaking countries where the use of Hypericum extracts has a long tradition differ from those from other countries although all trials used common diagnostic classifications (DSM-IV or ICD-10). With one exception [45], all trials from German-speaking countries were performed in private practices of general practitioners or specialists for internal medicine, neurology, and psychiatry, while most other trials were performed in more specialized centers such as academic psychiatric outpatient units. Depression with atypical or reversed vegetative features might be present more often in primary care outpatient populations. It has been hypothesized that Hypericum extracts might be particularly useful in this group of patients [46, 47]. However, it cannot be ruled out that some of the smaller German trials yielded exaggerated results.

A number of large observational studies – all performed in German-speaking countries – suggest that Hypericum extracts are effective and safe also in routine practice [48]. These studies have to be interpreted with caution as they were sponsored by manufacturers and seem to have been performed at least partly for marketing reasons.

The findings described so far refer to the treatment of acute episodes of depression. Such trials usually have observation periods between 6 and 12 weeks. A limited number of continuation studies are available [49–55]. These studies suggest that Hypericum extracts might successfully prevent relapse. Further continuation studies are desirable but such trials are expensive and difficult to perform.

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In Germany, Hypericum extracts are licensed and frequently used for the treatment of mild to moderate depressive disorders in adolescents (>12 years) [56, 57]. So far, only uncontrolled studies are available which suggest that Hypericum extracts are well tolerated and might be effective [58–60]. Randomized trials in children would be of major importance. Given ethical and methodological issues as well as marketing interests, however, it seems unlikely that manufacturers will sponsor such trials. Trials in children and adolescents are delicate. All children in both the experimental and the placebo group would have to receive adequate basic routine care (such as psychotherapy). In this situation, expected response rates in control groups are high and large sample sizes will be needed to detect additional medication effects. As drugs are already licensed and/or used in adolescents, manufacturers have limited interest in further trials. So researchers probably have to go for public funding.

What Is the Evidence Base for Other Indications?

Hypericum extracts have been tested in randomized trials for a number of other conditions. Closely related to the area of depression are particularly two recent and relatively large placebo-controlled German trials in patients suffering from somatization disorder (ICD-10 F45.0), undifferentiated somatoform disorder (F45.1), or somatoform autonomic dysfunction (F45.3) [61, 62]. Both trials showed statistically significant and clinically relevant effects over placebo after 6 weeks of treatment. An older, small German study in patients suffering from anxiety showed promising results [63]. Another positive older study of an oil preparation in patients suffering from 'psychovegetative disturbances' is difficult to interpret from today's point of view [64].

Several trials investigated conditions which seem less related to the most important indications of St. John's wort. No effects over placebo have been found in hyperactive children [65], social phobia [66], pain in polyneuropathy [67], and burning mouth syndrome [68]. A short report described positive findings from two trials in patients with herpes simplex genitalis and labialis [69]. Randomized trials also exist for combinations of Black Cohosh (*Cimicifuga racemosa*) and St. John's wort for climacteric complaints [70] and for a variety of combinations in depression or anxiety [71–73]. For other conditions only smaller observational studies or anecdotal evidence are available [10].

Is It Safe?

The amount of toxicological data on Hypericum preparations from the laboratory is limited. A relevant proportion of this work is on phototoxicity which is mainly due to napthodianthrones (hypericin and pseudohypericin) [10]. However, phototoxicity seems only of very limited clinical relevance in usual dose ranges [74]. The few data available on acute and subchronic toxicity do not reveal signs of a risk to the patient [10]. Ethanolic extracts have shown a weak mutagenic potential in the AMES test which probably can be attributed to the presence of quercetin [75]. The published data on reproduction toxicology are sparse and somewhat ambiguous. While several studies did not find effects on cognitive development, behavior, and growth, others found lower birth weight (see [76]) or liver and kidney damage [77]. Unless more research is available, Hypericum extracts should be avoided during pregnancy and lactation.

Data from post-marketing surveillance observational studies in medical practices in German-speaking countries show that Hypericum extracts are very well tolerated in routine use. A systematic review summarizing 16 observational studies including a total of 34,804 patients mostly suffering from depression found that the proportion of patients terminating treatment due to side effects varied in the 14 short-term studies from 0–2.8% and was 3.4 and 5.7% in the 2 long-term studies [48]. The proportion of patients reporting side effects was generally low, ranging between 0 and 5.9%. The most frequently reported side effects or adverse events were gastrointestinal symptoms. Increased sensitivity to light and skin symptoms in general were the second most often reported side effects. A variety of mental and nervous symptoms were also described in several studies. Serious adverse effects (requiring hospitalization) or interactions with other drugs were not reported in any study. As mentioned above, many of these observational studies have low methodological quality and should be interpreted with caution. Still, the overall results consistently show a very good safety profile when Hypericum extracts were prescribed by physicians.

The findings from observational studies are also consistent with the findings from randomized trials. On average, the number of patients reporting side effects and dropping out due to adverse effects among patients receiving Hypericum extracts is similar to those receiving placebo [42, 78]. According to the 2008 version of the Cochrane review on Hypericum for major depression, patients allocated to Hypericum extract were less likely to drop out from studies due to adverse effects than patients allocated to older standard antidepressants such as imipramine (OR = 0.25; 95% CI 0.13–0.46) or to SSRIs (OR = 0.53; 95% CI 0.34–0.83) [42]. Similarly, the proportion of patients reporting adverse effects was significantly lower (OR = 0.39; 95% CI 0.30–0.50 compared to older antidepressants, and OR 0.70; 95% CI 0.49–1.00 compared to SSRIs). The proportion of participants receiving Hypericum extracts reporting side effects is much higher in trials comparing Hypericum and standard antidepressants than in placebo-controlled trials [42, 78]. This is probably due to methodological reasons: In trials with standard antidepressants, patients are informed about a long list of potential side effects, and inquiry for adverse effects

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or events tends to be much more systematic than in placebo-controlled trials.

Systematic studies typically exclude patients with relevant comorbidity or the risk of interactions and apply Hypericum extracts within the recommended dosage schedule. Furthermore, some adverse effects might be too rare to occur even in larger observational studies. The number of published case reports on clinically relevant, direct adverse effects is low. A systematic review published in 2004 identified a total of 26 cases including well-documented cases reported to drug surveillance agencies [78]. 17 cases were skin or allergic reactions (erythema, dermatitis, urticaria, hyperesthesia, and neuropathy) and 9 were psychiatric reactions (mania, psychotic episodes, or anxiety). Although severe phototoxic reactions seem to be very rare events, patients should still be informed that Hypericum extracts increase light sensitivity. It must be kept in mind that some serotonin reuptake inhibitors also increase light sensitivity. Hypericum extracts and serotonine reuptake inhibitors (in particular nefadozon, paroxetine, and sertraline) should not be taken together although several of the reported cases of serotonin syndrome actually do not meet the criteria for such a diagnosis [74].

The clearly most relevant safety issue with hypericum extracts are interactions. Hypericum extracts are potent activators of the enzyme cytochrome P450 3A4 (CYP3A4) [79]. This enzyme plays a relevant role in the metabolization of a large number of drugs. Furthermore, Hypericum extracts also increase the activity of the P-glycoprotein, an ATP-dependent (adenosine triphospate) drug transporter which is responsible for an increase in excretion of drugs from the organism (e.g. via the mucosa of the gastrointestinal tract) [16, 79, 80]. Activations have also been described for further cytochrome enzymes [81]. It seems that hyperforin is the main component responsible for the interactions [17]. Therefore, in patients with relevant comedication, the use of extracts with low hyperforin contents and evidence for efficacy [18, 19, 82] could be an option.

A number of systematic reviews are summarizing different aspects of interactions related to Hypericum extracts [78, 80, 83–87]. In particular, Hammerness et al. provide a detailed review for the clinician [86]. Case reports provide clear evidence that relevant interactions occurred in patients receiving cyclosporin or other immunsuppressants after organ transplantation (e.g. [88–92]), protease inhibitors, and other virostatic agents used in HIV-infected patients (e.g. [93, 94]). While interactions with cytostatic agents have only been reported in experimental studies so far (e.g. [95]), most experts include cytostatic therapy among the contra-indications for Hypericum extracts. Patients receiving warfarin or other anticoagulant treatment must be monitored carefully as the efficacy of these drugs may be compromised [96]. Women taking oral contraceptives should be informed that a risk of interactions cannot be ruled out. There are a number of case reports on breakthrough bleeding and unplanned pregnancies associated with an intake of Hypericum extracts [78, 83, 97], but it is difficult to assess whether there is a causal link because these events also occur without comedication. The findings of experimental studies on hormone levels are not fully consistent [97–100].

Conclusion

St. John's wort is one of the oldest and best investigated medicinal herbs. Dried alcoholic extracts are the most important preparations on the market although a variety of other preparations are available. Depressive disorders are the best known and most widely investigated indication although the more traditional, broader indication 'psycho-vegetative disorders, depressive disorders, anxiety and/or nervous agitation' [6], including diagnoses such as somatoform disorders, might more adequately describe what Hypericum extracts are actually used for by many practitioners. The exact mechanisms of action are still unclear, but the available research clearly shows that various bioactive constituents contribute to the clinical effects reported, often in a synergistic manner. Hypericum extracts have consistently shown activity in pharmacological models related to antidepressant effects. Randomized clinical trials show that Hypericum extracts are more effective than placebo and similarly effective as standard antidepressant while having better tolerability in the acute treatment of major depressive episodes. The evidence from continuation studies is promising but limited. While Hypericum is widely used for depression treatment in adolescents in Germany, only uncontrolled studies are available. The few existing trials suggest effects over placebo in somatoform disorders; for other indications, the amount is insufficient to draw conclusions. The most important risk associated with Hypericum extracts are interactions with other drugs. Therefore, physicians need to be informed whether their patients take St. John's wort products. However, standard antidepressants also are associated with a large number of interactions with possibly relevant consequences [79, 101]. If the risk of interactions is adequately taken into account, high quality Hypericum extracts are an effective and safe tool in the hand of qualified health professionals in primary care.

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Conflict of Interest

The author has received reimbursement for travel expenses once for speaking at a symposium sponsored by a Hypericum manufacturer (Dr. Willmar Schwabe Arzneimittel, Karlsruhe, Germany).

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