DROŻDŻAŁ, Justyna, BARAŃSKA, Oliwia, CHAŃKO, Małgorzta, KRZACZKOWSKI, Adam, NIEDZIELSKA, Emilia, RĘDASZKA, Magadalena, SZUBA, Joanna, SZULAR, Zofia, WOJCZULIS, Tymon and ZIEMEK, Katarzyna. Hipercium species in the treatment of depression - a literature overview. Quality in Sport. 2025;42:60806. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.42.60806
https://apcz.umk.pl/QS/article/view/60806

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 07.05.2025. Revised: 10.06.2025. Accepted: 16.06.2025. Published: 17.06.2025.

Hipercium species in the treatment of depression - a literature overview

Justyna Drożdżał (JD)
Infant Jesus Clinical Hospital, Medical University of Warsaw,
4 Lindleya street, 02-005 Warsaw, Poland
https://orcid.org/0009-0008-1403-4777
justyna.drozdzal8@gmail.com

Oliwia Barańska (OB)
Bielanski Hospital
80 Ceglowska street, 01-809 Warsaw, Poland
https://orcid.org/0009-0008-5512-7048
oliwiafilomena@gmail.com

Małgorzata Chańko (MC)
Specialist Hospital Wejherow
10 dr. A. Jagalskiego Street, 84-200 Wejherowo, Poland
https://orcid.org/0009-0009-4571-0763
malgorzata.chanko@gmail.com

Adam Krzaczkowski (AK)
Infant Jesus Clinical Hospital, Medical University of Warsaw,
4 Lindleya street, 02-005 Warsaw, Poland
https://orcid.org/0009-0005-5851-587X
adam.krzaczkowski@onet.pl

Emilia Niedzieska (EN)
Central Clinical Hospital, Medical University of Warsaw,
1a Banacha street, 02-097 Warsaw, Poland
https://orcid.org/0009-0004-8946-1344
emilia.niedzieska@gmail.com

Magdalena Rędaszka (MR)
Infant Jesus Clinical Hospital, Medical University of Warsaw,
4 Lindleya street, 02-005 Warsaw, Poland
https://orcid.org/0009-0003-0679-6732
magda.red22@gmail.com

Joanna Szuba (JS)
Infant Jesus Clinical Hospital, Medical University of Warsaw,
4 Lindleya street, 02-005 Warsaw, Poland
https://orcid.org/0009-0000-7880-7523
joanna.szuba.15@gmail.com

Zofia Szular (ZS)
Infant Jesus Clinical Hospital, Medical University of Warsaw,
4 Lindleya street, 02-005 Warsaw, Poland
https://orcid.org/0009-0000-8854-1116
zszular@gmail.com

Tymon Wojczulis (TW)
Infant Jesus Clinical Hospital, Medical University of Warsaw,
4 Lindleya street, 02-005 Warsaw, Poland
https://orcid.org/0009-0002-0602-0427
t.wojczulis@gmail.com

Katarzyna Ziemek (KZ)
Infant Jesus Clinical Hospital, Medical University of Warsaw,
4 Lindleya street, 02-005 Warsaw, Poland
https://orcid.org/0009-0007-6947-0624
kasiaziemek@gmail.com

Abstract
Hypericum perforatum, commonly known as St. John's wort, has gained considerable attention as a herbal alternative in the treatment of mild to moderate depression. Given its favorable safety profile, natural origin, and evidence-based efficacy, it may represent a valuable support tool in mental health care, including among physically active individuals. The plant's therapeutic potential stems from the synergistic action of compounds such as hyperforin and hypericin, which modulate neurotransmitter systems and neuroinflammation. Clinical studies and meta-analyses confirm that H. perforatum demonstrates comparable effectiveness to conventional antidepressants, while showing fewer side effects. Although its interaction with other medications requires caution, the growing interest in phytotherapy highlights its relevance in supporting psychological well-being, especially in stress-prone populations, such as athletes or individuals seeking non-pharmacological interventions.

Key words
Hypericum perforatum; St. John's wort; herbal medicine; depression; phytotherapy; mental health; antidepressant effect; natural remedies.

Introduction

Over recent years, the incidence of depression has increased significantly. The disease significantly reduces the quality of life and leads to the exclusion of patients from professional activity [1]. Patients experience anhedonia, appetite and sleep disorders, concentration disorders, deficits of energy and suicidal thoughts [2] The WHO predicts that by 2030, depression will be the leading cause of disability worldwide. The effectiveness of current pharmacological treatments, such as SSRIs (e.g., fluoxetine) and SNRIs (e.g., duloxetine), is limited by their delayed onset of action and side effects [3] Selective serotonin reuptake inhibitors (SSRIs) are considered first-line drugs in the treatment of patients with depression. Unfortunately, patients experience many side effects such as nausea, vomiting, diarrhea, sexual dysfunction, blurred vision, headaches, hypotension and many others [2]. Due to these limitations, it is worth looking for a therapy that has a better tolerability profile. Number of antidepressant - controlled trials demonstrated that H. perforatum and its active ingredients, hypericin and hyperforin showed similar antidepressant properties to selective serotonin reuptake inhibitors but with milder and fever side effects [5].

Materials and methods

The authors conducted a literature review to collect current data on the chemical composition, mechanisms of action, and potential therapeutic applications of Hypericum perforatum (St. John's Wort), with particular emphasis on its antidepressant properties. Publications were searched in reputable databases such as PubMed, ScienceDirect, SpringerLink, and Google Scholar, focusing on works published between 2000 and 2024.

Specific keywords and logical operators were used, including: ("Hypericum perforatum" OR "St. John's Wort") AND ("antidepressant" OR "mechanism of action" OR "clinical trial" OR "phytochemistry" OR "pharmacology"). The search yielded a total of 186 publications, from which 64 articles were selected for full analysis based on their titles and abstracts.

Among them, 29 publications were included in the preparation of this paper, while the remaining were excluded due to thematic irrelevance.

General description

Hypericum perforatum which is commonly called St. John's wort (SJW) belongs to the Hypericum genus, the largest genus in the Hypericaceae family [6]. The plant is nowadays known all over the world, far from the original place of occurrence, which are Europe, western Asia and northern Africa [7]. SJW is a perennial reaching the height of about 50-100cm, whose name refers to John the Baptiste, as the plant traditionally blooms around the time of the feast [8] and the species name – perforatum comes from elliptical, translucent, leaves with perforated appearance [9]. The leaves, flowers and unopened buds collected in late spring or early summer must be dried immediately in warm weather to prevent degradation of their active ingredients [10].

The plant has two different types of secretory structures. The first one, known as pale or translucent glands, is found in the leaves, giving them a perforated appearance. These glands primarily store hyperforin and adhyperforin, along with other phloroglucinols, alkaloids, lipids, resins, and essential oils. The second type, seen as characteristic black spots, is located along the edges of the leaves and on the petals of the golden-yellow flowers; these are glands that contain hypericin and pseudohypericin [11].

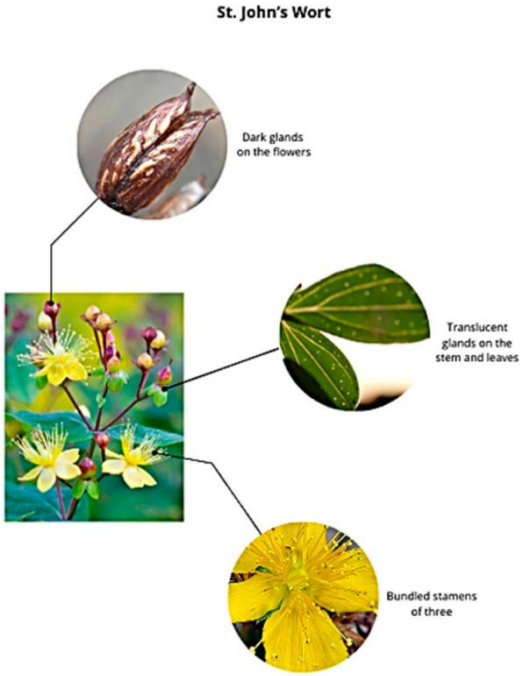

Figure 1. The main parts of H. perforatum [12].

Interest in the medical use of St. John's Wort was likely recorded already in ancient Greece; Hippocrates, and later Galen, studied the plant and recommended it for various ailments, including animal bites, menstrual pain, peptic ulcer disease, gastrointestinal disorders, wounds, burns, depression, and melancholy. Moreover, in *Historia Naturalis*, an ancient encyclopedia by Pliny the Elder that has survived from the times of the Roman Empire to the present day, SJW was also noted for its diuretic and anti-diarrheal properties [10]. Ongoing, extensive research on H. perforatum continues to expand knowledge of its pharmacological properties revealing additional benefits, such as antimicrobial, antinociceptive, antioxidant, anti-inflammatory [6] and analgesic effects [10]. It also demonstrates potential for use in the treatment of diseases such as icterus, liver and bile disorders, and insomnia [13]**.** Furthermore, studies have reported on the role of hypercin as an anticancer agent and its potential use in the treatment of neurodegenerative diseases [11] as well as its possible application as an alternative or complementary treatment for diabetes mellitus (DM) [2]. Despite its wide therapeutic profile, St. John's Wort is most commonly used today to treat mild to moderately severe depressive disorders [14] Due to its proven effectiveness in many studies and the growing popularity of natural remedies, it is also among the most frequently prescribed treatments for depression in Germany [6]. Hypericum perforatum also exhibits promising anxiolytic and anti-compulsive effects in preclinical and some clinical studies; however, further research is needed to confirm its efficacy in the treatment of OCD. [15]

Many studies over the years have confirmed that the active ingredients in St. John's wort exhibit antidepressant properties, and the mechanisms responsible for this are similar to those on which synthetic drugs are based. Moreover, it is worth emphasizing that the therapeutic effect of a medicinal plant is the result of the synergistic action of all its chemical/biological compounds, which often allows for its broader application [2].

Recent research has also indicated that adjunctive treatments such as combining medicinal plants with conventional drugs, can enhance the effectiveness of standard depression therapies. This synergistic effect may allow for lower doses of antidepressants, reducing the risk of unwanted side effects in sensitive patients. For instance, St. John's wort has been found to amplify the serotonergic effects of SSRIs. However, the opposite can also occur, potentially increasing adverse reactions. Therefore, it is crucial to exercise caution, as more extensive and rigorous studies are required to thoroughly investigate these interactions [16].

The dried herb, composed mainly of leaves, flowers and unopened buds is the part, that is pharmaceutically used [10]. H. perforatum contains phloroglucinols (primarily hyperforin, adhyperforin and furanohyperforin), naphthodianthrones (including mainly pseudohypericin and hypericin, as well as protohypericin, protopseudohypericin, cyclopseudohypericin and skyrin derivatives), flavonoids (glycosides of quercetin, such as hyperoside, rutin, isoquercitrin and quercitrin) and biflavones (I3, II8-biapigenin, amentoflavone). The three groups of chemical compounds mentioned above play a crucial role in its traditional medicinal uses[8]. Other compounds described in the literature include procyanidins (e.g., procyanidin B2, tannins), xanthones, essential

oils, phenolic acids (e.g., cholinergic acid, caffeoylquinic acid, p-coumaroylquinic acid), and free amino acids [9]. Currently standardized extracts from dried plant prepared with alcoholic solvents such as 60% ethanol or 80% methanol are used for the treatment of depression [17]. Hydroalcoholic extracts may contain up to 6% hyperforin, but the extraction process must be carefully controlled due to its instability and rapid degradation [18]. Chemical structures of hypericins and hyperforins are shown in Figure 2 [19].

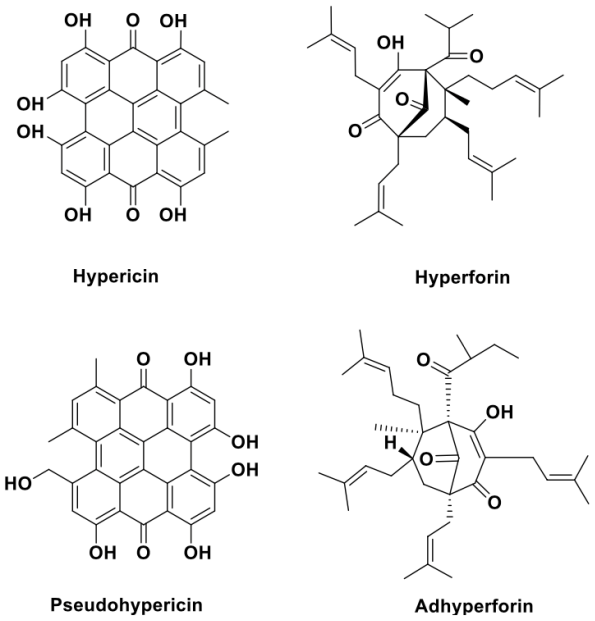

Figure 2. Chemical structure of hypericin and hyperforin [19].

Hypercium perforatum mechanism of action

St. John's wort has been shown in vitro to inhibit MAO-A and MAO-B activity while also blocking the reuptake of serotonin, dopamine, and noradrenaline. Additionally, it interacts with adenosine, GABAAA, GABABB, and glutamate receptors. Studies also suggest that its extract downregulates β-adrenergic receptors while upregulating 5-HT2 receptors [16]. The antidepressant properties of St. John's wort extract seem to be largely linked to the presence of hypericin, hyperforin, and various flavonoids, which contribute to its pharmacological effects [20].

One of the most important substance is hypercin. Hypericin has been identified as one of the primary potential active compounds. Its mechanism of action may involve the inhibition of the monoamine oxidase enzyme [19]. Monoamine oxidases (MAOs) are enzymes that regulate neurotransmitter levels, and while St. John's Wort (SJW) was initially thought to inhibit MAO activity, research suggests otherwise. Early *in vitro* studies showed that hypericin irreversibly inhibited both MAO-A and MAO-B at high concentrations, but later findings indicated that these concentrations were too high to be achieved *in vivo*, and at lower, nanomolar levels, the inhibitory effect was negligible. A 6-week clinical trial further confirmed that SJW had no significant impact on MAO-A density, suggesting that its antidepressant effects are not due to MAO inhibition [21]. So far, it has not been possible to link the different pharmacological effects of SJW to the activity of individual compounds. As a result, the components of the extract are believed to work together in a synergistic manner [18].

Studies have shown that St. John's wort extract may influence the regulation of serotonin receptors. Müller et al. (1997) observed an increase in the expression of 5-HT2 receptors in the frontal cortex of rats after 14 days of administration of a methanolic extract of *Hypericum*. Other studies (Teufel-Mayer & Gleitz, 1997) demonstrated a similar effect on 5-HT1A and 5-HT2A receptors after 26 weeks of treatment with high doses of St. John's wort [21]. Bukhari and Dar tested a standardized *H. perforatum* extract in the FST animal model of depression and concluded that its antidepressant-like effects were associated with selective serotonin reuptake inhibition [16].

St. John's wort exhibits therapeutic potential in treating depression by regulating gene expression and influencing the immune system. Five key genes associated with its antidepressant effects have been identified: AKT1, MAPK1, MYC, EGF, and HSP90AA1. These genes play a crucial role in neuroplasticity, oxidative stress, neuronal metabolism, and stress response [22]. An interesting mechanism of action can be observed in one species of Hypericum. Hyperibone J, the main component found in the flowers of Hypericum bellum, demonstrates both anti-inflammatory and antidepressant effects by binding to ADK in microglia, reducing its expression, and

subsequently inhibiting the ATP/P2X7R/Caspase-1 and TLR4/NF-κB pathways. These findings provide experimental evidence for the therapeutic potential of Hypericum bellum in treating depression [3].

Figure 3. Potential antidepressant mechanisms of action of H. perforatum[21].

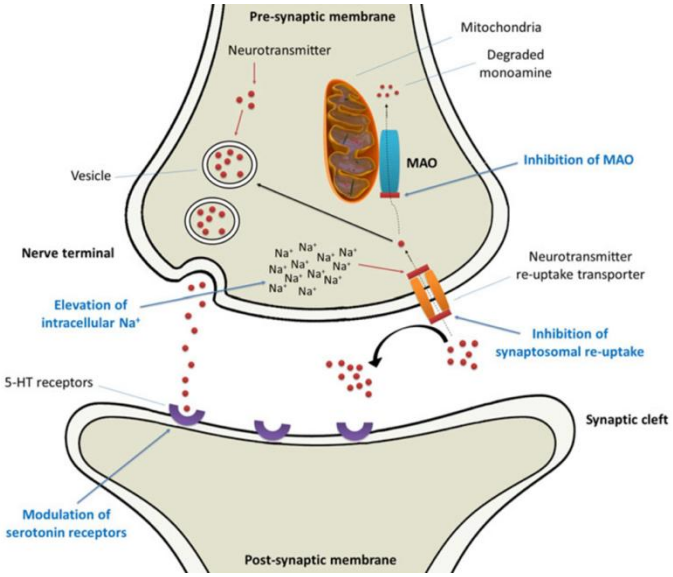

Table 1. Comparison of St. John's Wort vs Placebo in Clinical Trials

Authors (Year)	Number of Participants	Efficacy vs Placebo	Remission Rate	Tolerability
Linde et al. (2008)	5489	Superior	Higher than placebo	Better than placebo

Fava et al. (2005)	135	Superior	Moderate improvement	Well tolerated
Szegedi et al. (2005)	244	Equivalent	Similar	Good
Gastpar et al. (2006)	258	Superior	Higher	Well tolerated
Bjerkenstedt et al. (2001)	108	Comparable to standard antidepressants	37,4%	High
Papakostas et al. (2007)	Not determinated	Superior	Significant remission	Well tolerated

Brenner et al. (2000)	40	Superior	Higher remission rate	Better than placebo
Schrader et al. (2000)	240	Superior	Moderate improvement	Well tolerated
Moreno et al. (1997)	Not determinated	Superior	Improved remission	Good

Comparison of clinical trials evaluating the efficacy, remission rates, safety, and tolerability of St. John's Wort (Hypericum perforatum) versus placebo in the treatment of depression. The data summarized in the table are based on findings from two key review articles [23], [24].

Comparison of the use of St. John's Wort and Conventional Antidepressants in the Treatment of Depression

Due to the numerous side effects of synthetic antidepressants, St. John's Wort (*Hypericum perforatum*) is a promising natural alternative with potential antidepressant and sleep-inducing effects [6]. Several studies, such as those by Fava et al., Van Gurp et al., Moreno et al., and Singer et al., have shown that St. John's Wort (SJW) effectively lowers HAMD scores and alleviates depressive symptoms. Additionally, a meta-analysis by Linde and Mulrow, which examined 29 studies involving 5,489 patients, concluded that SJW is as safe as SSRIs for treating depression and offers superior safety with fewer side effects [25]. randomized controlled trial (RCT) on severe depression found no significant difference between the St. John's Wort (SJW) extract LI 160 and imipramine in terms of treatment response (RR 0.79; CI 0.45–1.37) or mean depression scale scores (SMD −0.17; CI −0.44–0.11). Overall, studies mainly focused on mild to moderate depression, with limited data on severe cases. Due to the small number of studies, it remains unclear whether SJW's effectiveness compared to antidepressants varies by depression severity. [26].

It is also worth considering the use of St. John's Wort in specific forms of depression, such as perinatal depression. During pregnancy, women often avoid conventional antidepressants, opting for natural treatments instead. Some studies have shown no negative effects of St. John's Wort on pregnancy, while others suggest potential side effects, such as drowsiness and colic in breastfed infants or an increased risk of developmental abnormalities [20]. In an analysis of the German GePaRD database, which included 496 pregnancies with prescriptions for St. John's wort between 2006 and 2016, the risk of developmental defects was 3.56 times higher in children whose mothers used St. John's wort during the first trimester. However, the results were not statistically significant [28].

Although SJW is classified as a dietary supplement by the FDA rather than a drug, it has been shown to be as effective, if not more so, than many standard depression treatments. Some randomized controlled trials even suggest that SJW may be a better option than fluoxetine due to its superior tolerability and safety profile [8]. Meta-analyses confirm that early SSRI therapy reduces the incidence of post-stroke depression (PSD) but increases the risk of bone fractures and nausea in the post-stroke population [29]. Therefore, the use of one of the Hypericum species may prove promising. The study using Hypericum androsaemum L., a representative of the Hypericum genus naturally occurring in the Mediterranean region, yielded interesting results. The study assessed the beneficial effects of H. androsaemum in an experimental model of post-stroke depression in animals. Protective effects of H. androsaemum in post-stroke depression were demonstrated in a mouse model, and this effect was linked to the antioxidant activity of its bioactive constituents [30]. Promising results have also been achieved by using St. John's Wort to alleviate postmenopausal depression symptoms. Seventy women participated in the study, and the results showed that treatment with Hypericum perforatum significantly reduced hot flashes, menopausal symptoms, and depression compared to the control group. At the end of the study, 80% of women in the intervention group were free of depression, while only 5.7% in the control group experienced the same improvement [31]. A In summary, we cannot definitively state that SJW is a better alternative to tricyclic antidepressants or SSRIs. Studies in which it was used in combination with tricyclic antidepressants or SSRIs suggest no additional impact on the effectiveness of depression treatment. Nevertheless, SJW appears to be a promising component of pharmacotherapy in the field of mental health [8].

Table 2. Differences between St. John's wort and the most common antidepressant groups [8]

PARAMETER	St. JOHNS WORT	TRICYCLIC ANTIDEPRESSANT (TCA)	SEROTONIN REUPTAKE INHIBITORS (SSRI)
Efficacy	Almost the same as conventional antidepressants	Effective treatment for depression	First-line treatment for depression
Safety	Same as conventional antidepressants	Safe use	Safe use
Most common adverse effect	Less than conventional antidepressants	Cardiac arrhythmia	Serotoninergic syndrome
Mechanism of action	Inhibition of the reuptake of serotonin monoamine oxidase activity reduces GABA binding.	Inhibition of the reuptake of serotonin and norepinephrine	Inhibition of the reuptake of serotonin
Cost	Low	Higher	High
Rate of discontinuation due to side effects	Low	Higher than St John's Wort	Higher than St John's Wort
Withdrawal symptoms rate	Low	Higher than St John's Wort	Higher than St John's Wort
Long-term antidepressant effects	Limited data	Well known long effectiveness	Well known long effectiveness
Approved by FDA	No	Yes	Yes
Drug interactions	HIV drugs, ciclosporin, tacrolimus, digoxin, oxycodone, warfarin, etc.	SSRI, anticholinergic, antihypertensive. antihistamine, etc.	NSAIDs, aspirin, warfarin, and all drugs increase serotonin, etc.

There are also reports suggesting that St. John's wort shows significant promise as a photosensitizer in photodynamic therapy (PDT) due to its active compound, hypericin. When exposed to light, hypericin generates reactive oxygen species (ROS), selectively inducing oxidative damage and cell death in cancer cells. Recent advancements aim to improve hypericin's stability, solubility, and selective targeting, enhancing its therapeutic efficacy and minimizing side effects. This has been achieved through innovative delivery systems, such as exosome-like nanovesicles derived from Hypericum perforatum, which could make PDT a more effective and selective treatment for cancer [32]

Drug interactions

Hypericum perforatum is a known inducer of CYP isoenzymes (CYP3A4, CYP2C9, CYP2C19) and also stimulates P-glycoprotein, which accelerates drug metabolism and can decrease plasma concentration of drugs

used in co-medication [9]. Therefore, long-term use of St. John's wort may lead to pharmacokinetic interactions with drugs that are metabolized by the same cytochrome isoenzymes, like HIV protease inhibitors (e.g. indinavir, ritonavir), HIV non-nucleoside reverse transcriptase inhibitors, oral contraceptives, anticonvulsants (e.g., carbamazepine, phenytoin), oral anticoagulant-vitamin K antagonists (warfarin), cyclosporin, tacrolimus, theophylline, digoxin [2]; care should be also taken when using it alongside methadone, simvastatin [9] and oxycodone[8] It is worth mentioning that potential interactions involving CYP or P-glycoprotein are not exclusive to Hypericum extract preparations; other antidepressants are also linked to multiple interactions that could result in significant complications [10].

Studies have shown that no clinically relevant pharmacokinetic interactions occur with low-hyperforin SJW extracts at doses up to 1 mg per day; therefore, SJW products with lower extract doses should be preferentially recommended to avoid further safety risks [18]**.** A pharmacodynamic interaction example is that Hypericum extract enhances serotonergic effects when used with antidepressants that influence serotonin (e.g., SSRIs such as sertraline, tricyclics, buspirone, or triptans), which may result in serotonin syndrome [33]. Serotonin syndrome is a serious and potentially life-threatening condition that occurs when serotonin receptors in the body become overstimulated. Its symptoms can range from mild side effects to severe toxic reactions, depending on the level of serotonin buildup caused by serotonergic medications.[34] Serotonin syndrome presents with a spectrum of symptoms ranging from mild (such as tremor, restlessness, headache, nausea, and diarrhea) to severe (including muscle rigidity, seizures, hyperthermia, and altered mental status). Moderate signs often include hyperreflexia, clonus, and agitation. In life-threatening cases, complications like rhabdomyolysis, renal failure, and disseminated intravascular coagulation may occur.[35]

Tolerability and safety

As mentioned earlier, one of the adverse effects is an increase in serotonin levels, particularly when combined with serotonin reuptake inhibitors (SSRIs) and monoamine oxidase (MAO) inhibitors, which may potentially lead to serotonin syndrome [8].

Adverse effects are usually mild and transient with the most commonly reported symptoms including digestive issues, dizziness, confusion, tiredness/sedation, allergic reactions, dry mouth[14]**,**[12]; there are also rare reports of its potential to trigger a hypertensive crisis and induce mania [8]. Furthermore, hypericin is phototoxic; however, when taken at a suitable dose - particularly with controlled hypericin content and with minimal UV exposure, the risk of photosensitization remains very low. Based on numerous studies, *H. perforatum* generally has a more favorable side-effect profile than synthetic and traditional antidepressants [6]**.** A European drug-monitoring study involving 3,250 patients found that the incidence of adverse events was only 2.4% for the clinical use of a commercial St. John's Wort extract in treating depression [18]. The Table 3. shows the comparison of the frequency of adverse effects between *H. perforatum* and synthetic/traditional antidepressants.

Symptom/Side Effect	St. John's Wort (%)	Synthetic/Traditional Antidepressants (%)	Comments
Nausea	5–10%	15–30%	Less frequent with St. John's Wort
Fatigue	10–15%	20–35%	Generally better tolerated
Insomnia	5–10%	10–20%	Similar frequency
Dry mouth	5–10%	15–25%	More common with antidepressants
Dizziness	5–12%	15–30%	Less reported with St. John's Wort
Weight gain	Rare (<5%)	20–30%	More prevalent with antidepressants
Sexual dysfunction	Rare (<5%)	30–50%	Very common with SSRIs and standard antidepressants
Anxiety or agitation	10%	15–25%	Slightly lower with St. John's Wort
Gastrointestinal issues	5–10%	20–30%	More common with antidepressants
Headache	5–10%	15–25%	Less frequent with St. John's Wort
Excessive sedation	Rare (<5%)	10–20%	More common with sedative antidepressants
Drowsiness	5–10%	20–30%	More prevalent with antidepressants
Excessive sweating	5–10%	15–25%	More reported with antidepressants
Confusion or disorientation	Rare (<5%)	10–15%	Less common with St. John's Wort
Tremors	Rare (<5%)	5–10%	Similar frequency
Phototoxicity	5–10%	Rare (<5%)	Exclusive to St. John's Wort in some cases
Tachycardia	Rare (<5%)	5–10%	Similar frequency
Hypotension	Very rare (<1%)	5–10%	More common with antidepressants

Table 3. The comparison of the frequency of adverse effects between *H. perforatum* and synthetic/traditional antidepressants [6]

However, before using St. John's Wort in combination therapy, it is crucial to carefully assess the patient's overall health and current medications to develop an effective treatment strategy that minimizes side effects and potential interactions [10].

Conclusion

Hypericum perforatum, commonly known as St. John's Wort, demonstrates considerable promise as a natural antidepressant, offering efficacy comparable to standard pharmacological treatments, particularly in cases of mild to moderate depression. Its favorable safety and tolerability profile, along with a multifaceted mechanism of action involving modulation of neurotransmitter systems, anti-inflammatory pathways, and neuroplasticity-related genes, underscores its therapeutic potential in the treatment of depressive disorders. The plant's long-established medicinal use, diverse pharmacological profile and lower incidence of adverse reactions make it a compelling alternative or adjunct to conventional antidepressants. While its ability to induce cytochrome P450 enzymes warrants caution when combined with certain medications, these interactions are generally manageable, especially with the use of low-hyperforin extracts. Overall, *H. perforatum* represents a valuable and well-tolerated option in the growing field of herbal pharmacotherapy for depression, with this review emphasizing its pharmacological effectiveness in correcting pathophysiological disturbances and alleviating depressive symptoms. The future of St. John's Wort appears highly promising, with numerous opportunities for advancement. Due to modern synthetic techniques and molecular biology approaches, the development of more structurally diverse and pharmacologically potent derivatives of St. John's Wort is expected to enhance its therapeutic applications.

All authors have read and agreed with the published version of the manuscript.

Author Contribution Statement:

The authors confirm contribution to the manuscript as follows:

- **Conceptualization**: JD, OB
- **Methodology:** MC
- **Software:** AK
- **Check:** OB, ZS, EN
- **Formal Analysis:** TW
- **Investigation:** KZ
- **Resources:** MR
- **Data Curation:** JS
- **Writing - Rough Preparation:** ZS
- **Writing - Review and Editing:** JD, AK
- **Visualization:** EN
- **Supervision:** JD
- **Project Administration:** OB

Funding Statement:

This study did not receive any external funding.. It was entirely supported by the personal contributions and resources of the authors.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: Authors have declared no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors used ChatGPT to enhance language and readability while preparing this article. After utilizing this tool, they reviewed and edited the content as needed and take full responsibility for the publication's substantive content.

References:

[1] E. A. Apaydin *et al.*, "A systematic review of St. John's wort for major depressive disorder," *Syst Rev*, vol. 5, no. 1, Sep. 2016, doi: 10.1186/s13643-016-0325-2.

[2] L. Dobrek and K. Głowacka, "Depression and Its Phytopharmacotherapy—A Narrative Review," Mar. 01, 2023, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/ijms24054772.

[3] T. Li *et al.*, "Hyperibone J exerts antidepressant effects by targeting ADK to inhibit microglial P2X7R/TLR4-mediated neuroinflammation," *J Adv Res*, 2024, doi: 10.1016/j.jare.2024.07.015.

[4] L. Dobrek and K. Głowacka, "Depression and Its Phytopharmacotherapy—A Narrative Review," Mar. 01, 2023, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/ijms24054772.

[5] N. Zirak, M. Shafiee, G. Soltani, M. Mirzaei, and A. Sahebkar, "Hypericum perforatum in the treatment of psychiatric and neurodegenerative disorders: Current evidence and potential mechanisms of action," Jun. 01, 2019, *Wiley-Liss Inc.* doi: 10.1002/jcp.27781.

[6] M. C. Otero *et al.*, "Documentary Analysis of Hypericum perforatum (St. John's Wort) and Its Effect on Depressive Disorders," Dec. 01, 2024, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/ph17121625.

[7] F. Di Pierro, P. Risso, and R. Settembre, "Role in depression of a multi-fractionated versus a conventional Hypericum perforatum extract," *Panminerva Med*, vol. 60, no. 4, pp. 156–160, Dec. 2018, doi: 10.23736/S0031-0808.18.03518-8.

[8] J. S. Canenguez Benitez *et al.*, "Advantages and Disadvantages of Using St. John's Wort as a Treatment for Depression," *Cureus*, Sep. 2022, doi: 10.7759/cureus.29468.

[9] M. Kenda, N. Kočevar Glavač, M. Nagy, and M. Sollner Dolenc, "Medicinal Plants Used for Anxiety, Depression, or Stress Treatment: An Update," Sep. 01, 2022, *MDPI*. doi: 10.3390/molecules27186021.

[10] N. Galeotti, "Hypericum perforatum (St John's wort) beyond depression: A therapeutic perspective for pain conditions," Mar. 22, 2017, *Elsevier Ireland Ltd*. doi: 10.1016/j.jep.2017.02.016.

[11] P. Rizzo, L. Altschmied, B. M. Ravindran, T. Rutten, and J. C. D'auria, "The biochemical and genetic basis for the biosynthesis of bioactive compounds in hypericum perforatum L., one of the largest medicinal crops in Europe," Oct. 01, 2020, *MDPI AG*. doi: 10.3390/genes11101210.

[12] A. Theodorakopoulou, I. Pylarinou, I. A. Anastasiou, and N. Tentolouris, "The Putative Antidiabetic Effect of Hypericum perforatum on Diabetes Mellitus," Jan. 01, 2025, *Multidisciplinary Digital Publishing Institute (MDPI)*. doi: 10.3390/ijms26010354.

[13] Z. İlhan, M. Zengin, O. K. Bacaksız, E. Demir, İ. H. Ekin, and M. A. Azman, "Hypericum perforatum L. (St. John's Wort) in broilers diet improve growth performance, intestinal microflora and immunity," *Poult Sci*, vol. 103, no. 12, Dec. 2024, doi: 10.1016/j.psj.2024.104419.

[14] J. Barnes, L. A. Anderson, and J. D. Phillipson, “St John’s wort (Hypericum perforatum L.) : a review of its chemistry, pharmacology and clinical properties,” *Journal of Pharmacy and Pharmacology JPP*, vol. 53, pp. 583–600, 2001.
[15] Z. Ayati, J. Sarris, D. Chang, S. A. Emami, and R. Rahimi, “Herbal medicines and phytochemicals for obsessive–compulsive disorder,” Aug. 01, 2020, *John Wiley and Sons Ltd*. doi: 10.1002/ptr.6656.
[16] I. s. Moragrega and J. L. Ríos, “Medicinal Plants in the Treatment of Depression: Evidence from Preclinical Studies,” Aug. 01, 2021, *Georg Thieme Verlag*. doi: 10.1055/a-1338-1011.
[17] G. Di, C. F. Borrelli, A. A. Izzo, and E. Ernst, “Review,” 2001. [Online]. Available: http://tips.trends.com0165
[18] S. Nicolussi, J. Drewe, V. Butterweck, H. E. Meyer Zu Schwabedissen, and H. E. Meyer, “Clinical relevance of St. John’s wort drug interactions revisited,” 2019, doi: 10.1111/bph.v177.6/issuetoc.
[19] S. Z. Nobakht, M. Akaberi, A. H. Mohammadpour, A. T. Moghadam, and S. A. Emami, “Hypericum perforatum: Traditional uses, clinical trials, and drug interactions,” *Iran J Basic Med Sci*, vol. 26, no. 9, pp. 1045–1058, Sep. 2022, doi: 10.22038/IJBMS.2022.65112.14338.
[20] V. Butterweck, “Mechanism of Action of St John’s Wort in Depression What is Known?,” 2003.
[21] N. Zirak, M. Shafiee, G. Soltani, M. Mirzaei, and A. Sahebkar, “Hypericum perforatum in the treatment of psychiatric and neurodegenerative disorders: Current evidence and potential mechanisms of action,” Jun. 01, 2019, *Wiley-Liss Inc.* doi: 10.1002/jcp.27781.
[22] Z. Xu, A. M. Rasteh, A. Dong, P. Wang, and H. Liu, “Identification of molecular targets of Hypericumperforatum in blood for major depressive disorder: a machine-learning pharmacological study,” *Chinese Medicine (United Kingdom)*, vol. 19, no. 1, Dec. 2024, doi: 10.1186/s13020-024-01018-5.
[23] R. C. Shelton, “St John’s wort (Hypericum perforatum) in major depression,” *Journal of Clinical Psychiatry*, vol. 70, no. SUPPL. 5, pp. 23–27, 2009, doi: 10.4088/JCP.8157su1c.05.
[24] R. Rahimi, S. Nikfar, and M. Abdollahi, “Efficacy and tolerability of Hypericum perforatum in major depressive disorder in comparison with selective serotonin reuptake inhibitors: A meta-analysis,” *Prog Neuropsychopharmacol Biol Psychiatry*, vol. 33, no. 1, pp. 118–127, Feb. 2009, doi: 10.1016/j.pnpbp.2008.10.018.
[25] X. Zhao, H. Zhang, Y. Wu, and C. Yu, “The efficacy and safety of St. John’s wort extract in depression therapy compared to SSRIs in adults: A meta-analysis of randomized clinical trials,” *Advances in Clinical and Experimental Medicine*, vol. 32, no. 2, pp. 151–161, Feb. 2023, doi: 10.17219/acem/152942.
[26] E. A. Apaydin *et al.*, “A systematic review of St. John’s wort for major depressive disorder,” *Syst Rev*, vol. 5, no. 1, Sep. 2016, doi: 10.1186/s13643-016-0325-2.
[27] D. Scuteri and B. Nephew, “St. John’s Wort usage in treating of perinatal depression.”
[28] W. Schäfer, N. Wentzell, T. Schink, and U. Haug, “Characterization of pregnancies exposed to St. John’s wort and their outcomes: A claims data analysis,” *Reproductive Toxicology*, vol. 102, pp. 90–97, Jun. 2021, doi: 10.1016/j.reprotox.2021.04.005.
[29] D. Richter *et al.*, “Selective serotonin reuptake inhibitors for the prevention of post-stroke depression: A systematic review and meta-analysis,” *J Clin Med*, vol. 10, no. 24, Dec. 2021, doi: 10.3390/jcm10245912.

[30] S. M. Nabavi *et al.*, “The water extract of tutsan (Hypericum androsaemum L.) red berries exerts antidepressive-like effects and in vivo antioxidant activity in a mouse model of post-stroke depression,” *Biomedicine and Pharmacotherapy*, vol. 99, pp. 290–298, Mar. 2018, doi: 10.1016/j.biopha.2018.01.073.

[31] A. Eatemadnia, S. Ansari, P. Abedi, and S. Najar, “The effect of Hypericum perforatum on postmenopausal symptoms and depression: A randomized controlled trial,” *Complement Ther Med*, vol. 45, pp. 109–113, Aug. 2019, doi: 10.1016/j.ctim.2019.05.028.

[32] X. Ma *et al.*, “Hypericum Perforatum-Derived Exosomes-Like Nanovesicles: A Novel Natural Photosensitizer for Effective Tumor Photodynamic Therapy,” *Int J Nanomedicine*, vol. 20, pp. 1529–1541, 2025, doi: 10.2147/IJN.S510339.

[33] S. Czigle, M. Nagy, P. Mladěnka, and J. Tóth, “Pharmacokinetic and pharmacodynamic herb-drug interactions—part I. Herbal medicines of the central nervous system,” *PeerJ*, vol. 11, p. e16149, Nov. 2023, doi: 10.7717/peerj.16149.

[34] N. Mikkelsen, P. Damkier, and S. A. Pedersen, “Serotonin syndrome—A focused review,” Aug. 01, 2023, *John Wiley and Sons Inc*. doi: 10.1111/bcpt.13912.

[35] C. Talton, “Serotonin Syndrome/Serotonin Toxicity,” *Federal Practitioner*, no. Vol 37 No 10, Oct. 2020, doi: 10.12788/fp.0042.