

St. John's Wort (*Hypericum perforatum*): A Review of its Potential Antidepressant Efficacy and Safety

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Abstract

Background: St. John's Wort (SJW), scientifically known as *Hypericum perforatum*, is widely utilized as an over-the-counter remedy for various ailments, particularly depression, despite lacking FDA approval. The active compounds in SJW, including hypericin, hyperforin, and flavonoids, are believed to alleviate depressive symptoms by inhibiting neurotransmitter reuptake. However, concerns regarding its safety arise from extensive drug-drug interactions, pointing to deficiencies in quality control and regulation of SJW distribution. **Methods:** This narrative review synthesizes existing literature on the therapeutic effects, safety profile, indications, and adverse effects of SJW in treating depression. It also examines the regulatory landscape surrounding SJW and highlights the necessity for standardized practices and comprehensive clinical trials. **Results:** SJW has shown efficacy in managing mild to moderate depression, with some studies suggesting it may offer benefits comparable to conventional antidepressants while exhibiting a more favorable side effect profile. However, significant safety concerns persist due to potential interactions with other medications, leading to adverse reactions such as serotonin syndrome. Current regulatory frameworks vary globally, with SJW classified as a dietary supplement in the

U.S. and subjected to stricter regulations in Europe. **Conclusion:** Despite its widespread use and potential therapeutic benefits, the safety and efficacy of SJW in treating depression remain inadequately substantiated by clinical evidence. Enhanced regulatory measures and rigorous clinical research are imperative to clarify SJW's role in depression treatment and ensure its safe application in clinical practice. Inclusion in pharmacopeias and adherence to good manufacturing practices could further improve the quality and safety of SJW products.

Keywords: St. John's Wort, Hypericums, *Hypericum perforatum*, Johnswort, Emotional Depression, Major Depressive Disorder.

Introduction

Depression is a disorder with more than 280 million around the world by 2023. World Health Organization (WHO) reported that 5% of adults are depressed being more common in females than males. Among females, it is more prevalent in those who have experienced pregnancy. Depression is a major cause of suicide and more than 700000 people die due to depression each year. It is one of the leading causes of death among youth aged 15-29 (WHO,2023). Disruptive mood dysregulation disorder, Major depressive disorder, dysthymia, premenstrual dysmorphic disorder, and Depressive disorder due to some other condition are the main categories of depression as classified by the American Psychiatric Association (Chand.S & Arif. H, 2023). Symptoms of depression include depressed mood along with any 5: sleep disturbance, worthlessness, change of appetite, suicidal intention, psychomotor disorder, attention impairment, fatigue, and interest reduction. Treatment of depression ranges from cognitive behavioral therapy to a comprehensive pharmacological regimen

Significance | This review provides widely used St. John's Wort as a supplement for depression despite controversies among scientists regarding its efficacy and safety.

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including Serotonin-Dopamine Activity Modulators, Selective serotonin or Serotonin/norepinephrine reuptake inhibitors, Tricyclic antidepressants, and Monoamine oxidase inhibitors, etc. Other modalities like electroconvulsive therapy are also used (Chand.S & Arif. H, 2023). Conventional pharmacological treatment of depression includes anticholinergic-like xerostomia, constipation, sweating, and urinary retention. CNS effects include headache, insomnia, sedation, GI effects like nausea, diarrhea, Weight gain, appetite changes, and hepatic dysfunction. Moreover, adverse effects related to the Cardiovascular system and Sexual disorders have also been reported in response to antidepressants (Kupfer D.J, 2005). This is where SJW comes to play its role. It is shown to have a relieving impact on the symptoms of depression without causing extensive side effects as that of pharmacological treatment.

St. John's Wort(SJW) is a plant that blooms in late June which is the same as the time of the feast of a Baptist, Saint John, hence its name. It is also known as hypericum, Klamath weed, or goat-weed in different regions but its scientific name is *Hypericum perforatum* (NCCIH,2020). This flowering plant is commonly found in Europe and Asia (Peterson. B & Nguyen. H,2023). this plant has been prominent in disease treatment for years. It has been used for some other neurological ailments including Alzheimer's Disease, topical use in skin diseases, pulmonary diseases including COVID, leishmaniasis, and many more ailments (Li JD et. al,2024)(Chakraborty S. et. al,2024)(Racziewicz I. et. al,2024)(Yıldırım A. et. al,2024). It has been used as a herbal medicine over the years but its major over-the-counter use is to relieve depression and anxiety. Despite its frequent use in this domain, it's still debatable for wide use among the population because of p450 enzyme interactions.

The trend of botanical herbal supplements has been rising lately. An estimate declares that by 2030 the sales of botanical herbal supplements will range from USD 92.84 billion to 204.14 Billion (Polaris Market). Moreover, that of St. John's wort has been estimated to reach USD 29 million by 2030 (Market Reports,2024). *Hypericum perforatum* has been the most popular Herbal supplement with a sale of billion dollars worldwide (Klemow. K.M. et.al, 2014). Besides customer demand by 2024, there are 778 PubMed research articles on searching St. John's Wort, *Hypericum perforatum* (Pubmed,2024). The interesting fact here is that despite its huge demand in the market it is still not approved by the FDA (Centre of Food Safety and Applied Nutrition,2021). Yet its off-label use for different ailments has been there for years. FDA considers it unsafe because of extensive p450 enzyme interaction thus interfering with the action of other drugs if being taken simultaneously by the patient. Thus, it becomes a double-sided sword, especially for patients on multiple medications (NCCIH,2020).

The use and role of SJW in depressive illness have been controversial in the literature. While some researchers talk about its similar mechanism of action to antidepressants at the same time others talk about the external validity of this statement. Thus, there is a dire need to re-examine the evidence to clarify its position as a treatment option (Shelton. R.C,2009). Furthermore, some clinical trials have shown that it shows 50% higher therapeutic implications as compared to placebo yet 18% lower as compared to pharmacological treatment of depressive illness (Gaster.B & Holroyd.J, 2000). That highlights the importance of this narrative review.

This review aims to provide an overview of existing literature regarding its use in depressive illnesses, safety profile, uses, and side effects. Moreover, we aim to highlight potential research gaps in this regard. This will ultimately enhance the clinical practice and literature on the medical use of herbal supplements especially SJW for curing depression.

Components and Mechanism of Action of SJW in Depression

Depression is a mood disorder with disturbed levels of neurotransmitters like serotonin (5-HT), norepinephrine (NE), dopamine (DA), glutamate, and brain-derived neurotrophic factor (BDNF). The decreased levels of these neurotransmitters in the synaptic cleft lead to the manifestations of symptoms of depression (Chand.S & Arif. H, 2023). Treatment of depression aims at the preservation of the required amount of neurotransmitters in the synaptic cleft via either inhibiting their reuptake from there or enhancing the release from the presynaptic membrane. SJW seems to act via the earlier mechanism i.e. inhibiting the reuptake of neurotransmitters from the synaptic cleft.

The key active compounds in SJW are hypericin and hyperforin, although, some other compounds like flavonoids and bioflavonoids, proanthocyanidins, polyglucinol derivative, chlorogenic acid, and naphthodianthrones are also present(Kholghi. G et. al,2022).

The main active compound regarding SJW's mechanism of action in depression is hypericin which works by inhibition of monoamine oxidase (MAO) (Bladt S & Wagner H,1994). Moreover, hypericin also acts via manipulation of cerebral CYP enzyme and neuroinflammatory signaling pathway. In animal models, it has been shown to upregulate m6A methyltransferase METTL3 and WTAP in the hippocampus. This leads to the anti-depressant effect due to hypericin (Lei. C et. al,2023). After hypericin, the second most prominent component in the mechanism of action of SJW is hyperforin. Amongst the phloroglucinol derivative hyperforin is thought to play a role in relieving depression by affecting the hemostasis of neurotransmitters. It is thought to inhibit the reuptake of neurotransmitters like serotonin, noradrenaline, dopamine, glutamate, and GABA (Di Carlo.G. et.al, 2001)(Butterweck. V, 2003). This ultimately leads to higher levels of

these neurotransmitters in the blood, thus, relieving symptoms of depression. The mechanism of inhibiting the serotonin uptake by hyperforin has been shown in animal models. Hyperforin is shown to increase sodium ion concentration like monensin but via a slightly different mechanism. Contrary to monensin, hyperforin does not elevate the concentration of sodium ions at high levels (Singer.A et al, 1999).

Reuptake of substances like L-glutamate and γ -aminobutyric acid is also inhibited by SJW (Oliveira A.I. et al , 2016). Yet, it poses a fluctuating impact on the levels of neurotransmitters. In depression, neurotransmitters like acetylcholine and glutamate play an important role while SJW leaves a dualistic impact on the cholinergic system (Kholghi. G et. al,2022). Regarding nor-epinephrine, its levels are thought to be increased due to the inhibition of monoamine oxidase (MAO) by St. John's Wort. Moreover, it has also been reported to stimulate molecules like pregnane-X-receptor (PXR) cytochromes which in turn stimulate the p450 including P glycoprotein and CYP3A4 (Peterson. B & Nguyen. H, 2023).

Besides that flavonoids like quercetin, luteolin, and kaempferol in SJW are also known for their anti-depressive activity (Greeson JM et al, 2001). Flavonoids are bioactive polyphenols known to increase BDNF and neurotransmitters. They contribute to neurogenesis pathways like noradrenergic, GABAergic, serotonergic, dopaminergic, MAO, and tropomyosin receptor kinase B. Moreover, they also modulate the receptors and perform anti-oxidant action. This increases the growth of nerves and neurotrophic factors in the brain. By this mechanism, flavinoids relieve subclinical depression(Pannu. A et. al,2021).

This intricate pattern of action SJW calls for more research to elucidate the sequence of events in these pathways along with the enzymes involved like hyperforin synthase. Single-cell RNA sequence approach should be used to discover the gene and full pathways (Wu. S & Tatsis E.C , 2024). The concentration of hypericin and hyperforin in different formulations and products of SJW creates inconsistent effects. Further CYP-450 interaction also limits the use of SJW. Thus, a clear-cut statement on its use backed up by a well-researched mechanism of action can play a role in its approval as an antidepressant.

Indications, Safety, Side Effects, and Drug Interactions, Comparison with Conventional Treatment:

In some trials, SJW has been shown to have a curative effect on depression but the evidence is low quality and is not significant enough to lay the basis of a fact (Maher. A.R et al,2016). The use of SJW in a variety of depression is shown in Table 1.

The use of SJW is fruitful in the treatment of mild-moderate depression, although information regarding its effect on the severity of depression is yet to be explored (Ng. Q.X et al,2007) (Benitez. J.S.C et. al., 2022)(Kasper.S et al,2004). It has also been effective in <https://doi.org/10.25163/ahi.4110003>

somatoform disorders, depressive upset, restlessness, nervousness, exhaustion, and sleep disturbances. Its extensive anti-inflammatory and antioxidative effects have also enabled it to be a better treatment option for patients of depression having coronary heart disease(Saller.R et al ,2003). Greatly it has been used to cure depression especially in postpartum in the past (Allaire AD et.al , 2000)(Dennehy C et.al,2010). Limited studies are there on SJW's efficient action, therefore more studies are required for the warranted use of SJW as a treatment of depression (Josey ES & Tackett RL,2017).

The safety and efficacy of SJW are remarkable when used as monotherapy. Grinding of flowers as well as dried leaves of plants forms the medicinal form of SJW. It is used orally, IV, or topical but the dose and potency vary in various forms. Oral use via capsules is the most common mode of administration. Capsules of 300 mg are taken three times a day and contain 0.3% hypericin content (Peterson. B & Nguyen. H,2023).

Side effects and drug-drug interactions of SJW are of great importance due to its wide usage. SJW acts as a double-sided sword and worsens depression in some patients (NCCIH, 2017). SJW-induced nausea, rash, xerostomia, headache, and photosensitivity when used for depression have also been reported (Benitez. J.S.C et. al., 2022)(NCCIH, 2017)(Gaster B & Holroyd J.,2000). SJW when taken with other drugs for depression can lead to serotonin syndrome, diarrhea, hypertension, fever, hallucinations, and agitation. Moreover, the worsening symptoms in the schizophrenics and Bipolars have also been reported as shown in Figure 1. Extensive interactions of SJW other than antidepressants have been reported with Oral contraceptives, immunosuppressants, cardiac glycosides, opiates, anti-HIV, chemotherapeutics, and anticoagulants (NCCIH, 2017). Withdrawal symptoms of methadone can be accentuated via concurrent use of SJW (Eich-Höchli.D et al,2003). SJW is contraindicated in pregnancy, breastfeeding, severe depression, BPD, and poly-therapy with other antidepressants.

Some studies have also reported that SJW has high molecular weight and poor solubility which leads to its low levels in brains as compared to anti-depressants after the dose. This ultimately impacts the pharmacological action of SJW. The brain concentrations of all these high-molecular-weight, poorly water-soluble compounds after pharmacologically effective doses of the extracts are therefore far below those effective on neurotransmitter receptors and the mechanisms that are important in the central effects of conventional, pharmacologically related drugs (Caccia S & Gobbi M , 2009).

Scientists have mixed results regarding the use of SJW and its comparison with conventional treatment for depression via clinical trials (NCCIH, 2017). SJW owing to its tolerability and safety has shown to be superior to fluoxetine. Yet, it showed no increased efficacy of treatment when used in combination with TCA, SSRI,

Table 1. Uses of SJW in Depression

Study	Use of SJW in Depressive Illness
(Benitez, J.S.C et. al., 2022)	Post-menopausal depression
(Ng.Q. X et al,2007)	Mild-moderate depression.
(A.L.Miller,1998)	Seasonal affective disorder(SAD)
(Kasper.S et al,2004)	Continuation and long-term maintenance treatment after acute treatment of mild to moderate depression
(Saller.R et al ,2003)	Depressive upset and depression
(Allaire AD et.al , 2000)	Postpartum depression
(Dennehy C et.al,2010)	

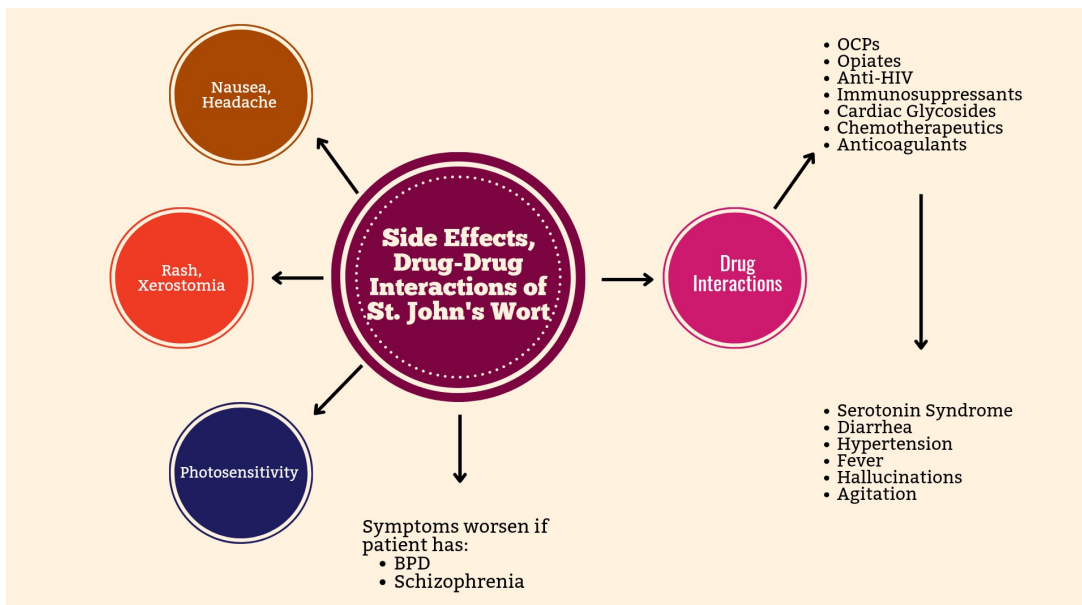


Figure 1. Adverse Effects and Drug Interactions of St. John’s Wort.

and antidepressants (Benitez. J.S.C et. al., 2022). SJW has been shown to have relative efficacy as SSRI, more effectiveness than placebo, and a good prospect as continuation therapy in patients with mild-moderate depression (Ng. Q.X et al,2007) (Benitez. J.S.C et. al., 2022)(Kasper.S et al,2004). Regarding anti-cholinergic and cardiac side effects, SJW is superior to anti-depressants like MOA-I and TCAs (Josey ES & Tackett RL,2017).

Regulatory Status and Quality Control and Future Directions:

SJW is currently unregulated at a very large scale. In the United States of the America, it is available as a herbal supplement while in France it is banned. It has not yet been approved by FDA. Although it is being regulated very strictly in Germany and most of European countries. Pharmaceutical industries also play a great role in its regulation. Clear regulation on SJW should be given by the Dietary Supplement Health and Education Act (DSHEA). Moreover, labeling and marketing regulations regarding SJW should be formulated. The European Medicines Evaluation Agency (EMA) has also warned about the potential drug interactions of SJW, despite its free availability and access. The traditional herbal medicinal products directive (THMPD) should register SJW after reviewing its status as a supplement being used widely for the cure to depressive illness.

Besides regulations of SJW, its quality should also be standardized. A certain amount of hypericin and hyperforin content should be in all batches of a product. All such details should be clearly on the label. Good Manufacturing Practices (GMP) play an important role in the availability of pure, potent, and safe formulations of SJW. Contaminant testing against heavy metals, microbes, or pesticides should also be done before its dispense. Products of SJW should be checked against international standards before their dissemination in the market. Moreover, SJW should be included in pharmacopeias to enhance its quality. Moreover, issues like adulteration and batch-to-batch consistency should be maintained by inculcating analytic methods. Further, the bioavailability of active components and the shelf life of SJW should also be defined.

Some meta-analyses and systematic reviews have reported the safe use of SJW in mild-moderate depression. Whereas, variable potency in different formulations, large-scale and long follow-up studies for severe depression are some limitations in the wide-range use of SJW against depression. Thus, the need of hour is extensive SJW trials especially therapy-oriented clinical research to make the picture clear regarding its use in the treatment of depression. (Saller.R & Rostock. M, 2012)

Conclusion

SJW has been used over the counter as a supplement for depression. Its sales depict its extensive use while research on the safety and efficacy is still scarce. Researchers are not being able to state any **clear-cut statement regarding its safety**. It is because of its intricate <https://doi.org/10.25163/ahi.4110003>

mechanism of action, adverse effects, undiscovered nature, and wide drug-drug interactions. This calls for research on SJW as the gap is evident. Clarity on the uses and adverse effects of SJW will lead to the regulation of its dispense and use. This also highlights the importance of regulation and law enforcement in the market of SJW.

Author contributions

All authors made equal contributions to the study design, statistical analysis, and drafting of the manuscript. The corresponding author, along with the co-authors, reviewed and approved the final version of the article prior to submission to this journal.

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Competing financial interests

The authors have no conflict of interest.

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