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Therapeutic applications of *Hypericum perforatum* (St. John's wort) for treating anxiety and depression: integrative review

Aplicações terapêuticas do *Hypericum perforatum* (erva-de-são-joão) no tratamento da ansiedade e depressão: revisão integrativa

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Abstract

Hypericum perforatum, known as St. John's wort, is a popular medicinal plant recommended in traditional Chinese medicine and prescribed for depression in European countries. However, conflicting data were observed regarding its benefits and risks. This study aimed to evaluate phytopharmaceuticals containing *Hypericum perforatum* extracts for anxiety and depression treatment. An integrative review was performed by searching Literatura Latino-Americana e do Caribe em Saúde (LILACS), Scientific Electronic Library Online (SciELO), and Publisher Medline (PubMed) databases and included studies in Portuguese, English, and Spanish from 2017 to 2022. Randomized clinical trials confirmed the efficacy of the *Hypericum perforatum* extracts compared with placebo on mild and moderately severe depression. Further randomized controlled studies demonstrated similar efficacy to conventional antidepressants for anxiety and mild to moderate depression. The study concludes the need for more studies to evaluate the efficacy of *Hypericum perforatum* extracts, especially concerning adverse effects, risks, and drug interactions.

Keywords: Anxiety; Depression; Phytopharmaceuticals; *Hypericum perforatum*.

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Resumo

O *Hypericum Perforatum*, também conhecido como erva de São João é uma planta medicinal popular recomendada pelos praticantes da medicina tradicional chinesa e amplamente prescrita para a depressão em muitos países europeus. No entanto, existem dados conflitantes sobre seus benefícios e riscos. O objetivo deste estudo foi avaliar os benefícios e riscos dos fitoterápicos contendo *Hypericum perforatum*. no tratamento da ansiedade e depressão. Realizou-se uma revisão integrativa a partir de artigos publicados em nas bases científicas Literatura Latino-americana e do Caribe em Saúde (LILACS), *Scientific Electronic Library Online* (SciELO) e *Publisher Medline* (PubMed) entre os anos de 2017 a 2022 nos idiomas português, inglês e espanhol. Evidências de ensaios clínicos randomizados confirmaram a eficácia dos extratos de *Hypericum Perforatu.* em relação ao placebo no tratamento da depressão leve a moderadamente grave. Outros estudos randomizados controlados forneceram algumas evidências de que os extratos da planta são tão eficazes quanto alguns antidepressivos convencionais na ansiedade e depressão leve a moderada. Conclui-se que há a necessidade de mais estudos para avaliar a eficácia dos extratos de *Hypericum Perforatum,* principalmente no que se refere aos eventos adversos, possíveis riscos e interações com outros medicamentos.

Palavras-chave: Ansiedade; Depressão; Medicamento fitoterápico; *Hypericum perforatum*.

INTRODUCTION

Medicinal plants are vegetable species culturally used for nutrition and medicinal therapies.[1] Several societies demonstrated the importance of using medicinal plants and accumulated experiences and knowledge regarding their use, action mechanisms, and treatment effects for physical and psychoemotional illnesses.[2, 3]

Evidence points to the use of medicinal plants throughout human history, starting from Neanderthal men in the Paleolithic period who relied on nature to provide resources for survival.[4, 5] Medicinal plants were also used by the Babylonic civilization, which had an extensive collection of plant- and animal-based drugs as solutions, enemas, suppositories, ointments, and pills. Moreover, a traditional Indian system of medicine named Ayurveda has been using these compounds for over five thousand years.[6]

The knowledge of medicinal plants properties has been used to produce phytopharmaceuticals, which are natural or synthetic medicines obtained exclusively from the raw material of active plants.[7] Ethnopharmacological surveys, technical-scientific documentation, or clinical evidence validated the efficacy, safety, risks, and quality of phytopharmaceuticals.[8] Medicines with isolated active substances, regardless of origin, and the association of isolated substances with plant extracts are not considered phytopharmaceutical.[9]

The easier accessibility to medicinal plants in communities reinforced phytopharmaceuticals as essential resources for treating different pathologies, in addition to possibly reduced costs

and significant benefits compared with allopathy (i.e., conventional medicine treatment for illness symptoms).[10]

The *Hypericum perforatum* (St. John's wort or hypericum) has a high medicinal potential.[11,12] The species from the *Hipericaceae* family presents organic and aqueous extracts vastly used for treating mild, moderate, and severe unipolar depression.[13] The indications for its use were based on empirical studies[14] followed by clinical trials and anxiolytic and anti-depressive assessments, confirming that aqueous extracts were as effective as conventional antidepressants and led to fewer side effects.[15]

The phytopharmaceutical produced with *Hypericum perforatum* is one of the few natural antidepressants influencing dopamine and norepinephrine brain levels and is considered an efficient alternative for depression treatment.[16] In Brazil, *Hypericum perforatum* is commercialized in street markets and was recently added as a component in industrialized products indicated for anxiety and depression treatment.[17]

This study was motivated by the increased interest in medicinal plants and the high consumption of phytopharmaceuticals. Our results may contribute to the knowledge on the benefits and risks of the *Hypericum perforatum*, especially as a therapeutic recommendation for anxiety and depression. Thus, this study aimed to evaluate the benefits and risks of phytopharmaceuticals containing Hypericum perforatum for anxiety and depression treatment.

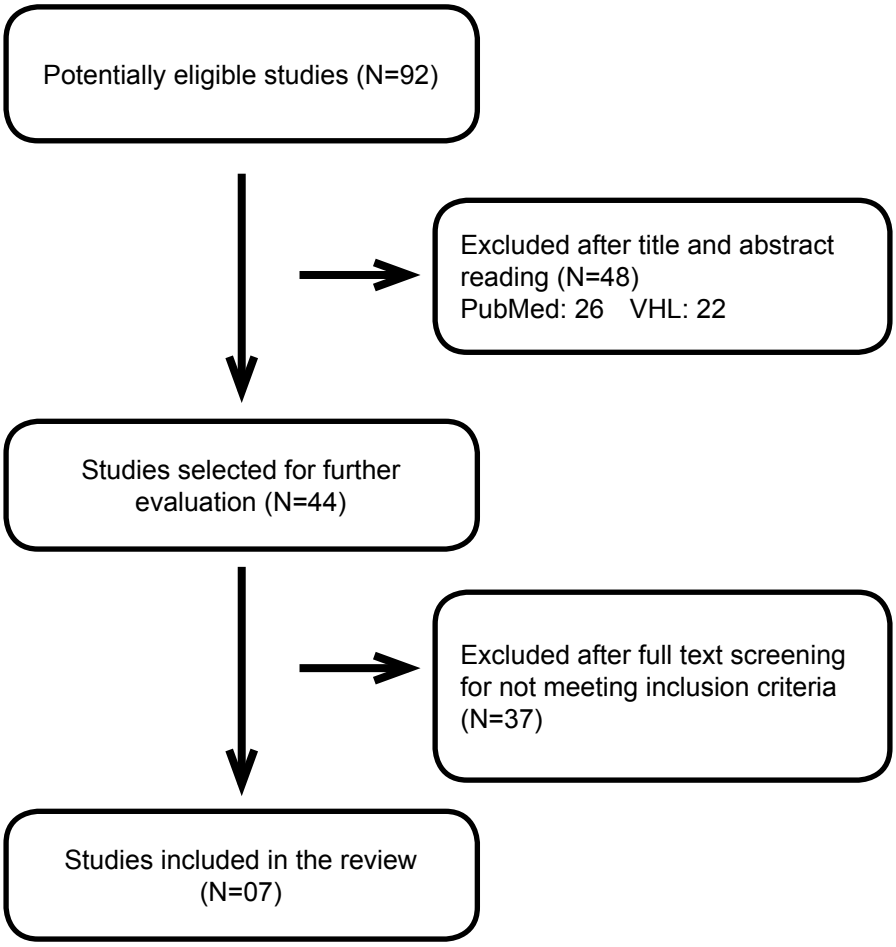
METHODS

This study was an integrative review using data from indexed articles searched on the Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS), and Publisher Medline (PubMed) databases. Inclusion criteria were studies from 2017 to 2022 published in Portuguese, English, or Spanish (Figure 1). Health sciences descriptors were used in the searches: anxiety, depression, phytopharmaceuticals, and *Hypericum*. Searches were performed with isolated and combined descriptors. Book chapters, monographs, thesis, dissertations, editorials, and publications that did not meet the study criteria were excluded.

RESULTS

After checking for inclusion and exclusion criteria, the characteristics of the selected articles are described in Table 1.

Figure 1. Flowchart of the process for study selection



PubMed: Publisher Medline; VHL: Virtual Health Library

Table 1. Characterization of the included studies

Author/ Year	Title	Aim	Main findings
Apaydin et al. (2017)	A systematic review of St. John's wort for major depressive disorder.	To evaluate the use of St. John's wort for major depressive disorder (MDD) treatment.	St. John's wort monotherapy for mild to moderate depression was superior to placebo for improving depression symptoms and did not show a significantly difference from conventional antidepressants.[18]

Moreno et al. (2017)	*Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample	To evaluate the efficacy and safety of *Hypericum perforatum* compared with fluoxetine.	*Hypericum perforatum* was less effective than fluoxetine and placebo. Both drugs were safe and well tolerated.[19]
Ng & Venkatanarayanan (2017)	Clinical use of *Hypericum perforatum* (St John's wort) in depression: A meta-analysis.	Review of clinical trials comparing St. John's wort and selective serotonin reuptake inhibitors (SSRIs) in patients with depression.	St. John's wort showed efficacy and safety similar to SSRIs for patients with mild to moderate depression.[20]
Soleymani et al. (2017)	Clinical risks of St John's wort (*Hypericum perforatum*) co-administration.	To evaluate pharmacokinetic changes of conventional medications used concomitantly with St. John's wort preparations.	St. John's Wort preparations showed clinical interactions with several classes of conventional medicine.[21]
Eatemadnia et al. (2019)	The effect of *Hypericum perforatum* on postmenopausal symptoms and depression: A randomized controlled trial.	To test the effects of *Hypericum perforatum* in heatwaves, menopause symptoms, and depression in women with postmenopause.	*Hypericum perforatum* treatment reduced heatwaves, menopause symptoms, and depression in women with postmenopause.[22]
Zirak et al. (2019)	*Hypericum perforatum* in the treatment of psychiatric and neurodegenerative disorders: Current evidence and potential mechanisms of action.	Review of *in vitro*, *in vivo,* and clinical evidence on the efficacy, safety, and action mechanisms of St. John's wort and its active compounds in treating psychiatric and neurodegenerative disorders.	St. John's wort showed potent anti-depressive effects and demonstrated to be an effective and safe treatment.[23]
Adibelli et al. (2022)	St. John's wort (*Hypericum perforatum*)- Related Acute Kidney Injury	To report the case of an acute kidney injury (AKI) in a patient who used *Hypericum perforatum* infusion as treatment for sleeping disorder.	The patient developed acute kidney injury (AKI) after ingesting infused tea of *Hypericum perforatum*.[24]

Studies showed the therapeutic efficacy of *Hypericum perforatum* for treating depression. Ng and Venkatanarayanan analyzed 27 clinical trials with a total of 3,808 patients comparing

the use of St. John's wort with selective serotonin reuptake inhibitors (SSRI).[20] St. John's wort presented a similar response, remission of symptoms, and significantly less discontinuation (i.e., abandonment) compared with standard SSRI treatments. The authors concluded that the long-term efficacy and safety of *Hypericum perforatum* are limited since studies lasted four to twelve weeks.[20]

Apaydin et al. demonstrated similar results when evaluating St. John's wort in adults with depression,[18] showing greater efficacy and safety than placebo and standard antidepressants. These findings were valid even with varying effects according to the depression severity. St. John's wort monotherapy for mild and moderate depression was superior to placebo, significantly improving the symptoms of patients.[18]

However, Moreno et al. observed different results evaluating the efficacy and safety of St. John's wort compared with fluoxetine in an eight-week double-blind study including patients with mild to moderate depression.[19] Seventy-two outpatients were randomly selected to take 900 mg/day of St. John's wort phytopharmaceutical, 20 mg/day of fluoxetine, or placebo. The analysis did not show differences between the average scores of the three groups. Patients who received the phytopharmaceutical had the lowest remission rates (12%) compared with fluoxetine (34.6%) and placebo (45%). The study concluded that St. John's wort was less efficient than fluoxetine and placebo, and all drugs were safe and well tolerable.[19]

A randomized-controlled study by Eatemadnia et al. tested the effect of *Hypericum perforatum* on depression in 80 women with post-menopause, aged 45 to 60 years.[22] Groups received 270 to 330 µg of *Hypericum perforatum* (n = 40) or placebo (n = 40) tablets three times a day for two months. Questionnaires were collected two, four, six, and eight weeks after intervention. Results from 70 women showed that *Hypericum perforatum* treatment reduced menopause symptoms and depression in women with post-menopause.[22]

Zirak et al. reviewed *in vitro*, *in vivo*, and clinical evidence regarding the efficacy, safety, action mechanisms, and active compounds of St John's wort, for the treatment of psychiatric and neurodegenerative disorders.[23] Controlled trials using antidepressants showed that *Hypericum perforatum* and its active compounds, hypericin and hyperforin, presented antidepressant properties similar to tricyclic antidepressants and SSRIs but with fewer and milder side effects. However, clinical evidence on *Hypericum perforatum* efficacy in other psychiatric and neurodegenerative disorders was not robust.[23]

The study of Soleymani et al. evaluated pharmacokinetic changes of conventional medications concomitant with St John's wort formulas.[21] St John's wort formulas presented clinical interactions with several classes of conventional medication, such as immunosuppressants, anticancer agents, cardiovascular medication, oral contraceptives, and lipid-reducing agents, causing life-threatening events. The information label on products with the plant compound must provide

information about interaction risks. Hyperforin seems to be the main ingredient responsible for inducing the activity of Cytochrome P450 and P-glycoprotein by St John's wort. Therefore, products without hyperforin may be candidates to decrease medication interactions of St John's wort.[21]

Phytopharmaceutical products were reported as nephrotoxic due to different mechanisms. Adibelli et al. reported a study case of an acute kidney injury (AKI) in a patient who ingested tea infusions of *Hypericum perforatum* as a treatment for sleep disorders.[24] The patient developed acute renal failure and underwent hemodialysis. The kidney function was reestablished after a week and showed regular function upon hospital discharge.[24]

Clinical guidelines for anxiety and depression treatment in several countries omit *Hypericum perforatum* or advise against its use due to its unknown therapeutic effects.[18, 19] The lack of knowledge from patients and professionals about using this medicinal plant is concerning, especially considering the potential interactions between *Hypericum perforatum* and conventional medicine.[23, 24]

Nowadays, despite the evidence on the efficacy of standard extracts of *Hypericum perforatum*, authorized products hold a "low level" label indication for "slightly low mood symptoms and mild anxiety".[20, 21] This occurs due to loose regulatory structures for phytopharmaceuticals that only authorizes products for self-treatment addressing lower and auto-limited conditions, which is not appropriated for depression.[22, 23, 24]

CONCLUSIONS

The *Hypericum perforatum* chemical composition has been studied, and its pharmacological activities include antidepressant, antiviral, and antibacterial effects, providing supporting evidence for its traditional uses. Most pharmacologic activities are attributed to hypericin and hyperforin, the main components responsible for the anxiolytic and anti-depressive activities.

Safety and tolerability studies showed that *Hypericum perforatum* preparations have better profiles than synthetic antidepressants, being indicated for anxiety and mild or moderate depression. We highlight the need for further studies to evaluate the efficacy of *Hypericum perforatum* extracts, especially regarding adverse effects, risks, and interactions with other drugs.

CONFLICT OF INTERESTS

Nothing to declare.

AUTHOR CONTRIBUTIONS

ALSC, **HGQM**, **KRBS**, **LCDN**, **LCPG**, and **PGPM**: study design, article writing, and final version approval; **MLCP** and **TKC**: supervisor, proofreading, and final version approval.

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