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File: ■ St. John's Wort (*Hypericum perforatum*, Hypericaceae)
■ Depression
■ Meta-analysis

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RE: Meta-analysis Finds Standardized St. John's Wort Extracts as Effective as Conventional Antidepressants

Ng QX, Venkatanarayanan N, Ho CYX. Clinical use of *Hypericum perforatum* (St John's wort) in depression: A meta-analysis. *J Affect Disord*. 2017;210:211-221.

St. John's wort (SJW; *Hypericum perforatum*, Hypericaceae) aerial parts are a popular treatment for depression, and many countries in Europe prescribe SJW for that purpose. According to the authors, SJW has been well researched; however, the results are conflicting. The last large published meta-analysis was conducted in 2008, and it found SJW superior to placebo and similar to conventional antidepressants. Since then, additional research has emerged. Hence, the objective of this systematic review and meta-analysis was to provide an updated analysis.

The following databases were searched from January 1, 1960, through May 1, 2016, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines: PubMed; Ovid; Clinical Trials Register of the Cochrane Collaboration Depression, Anxiety and Neurosis Group (CCDANTR); Cochrane Field for Complementary Medicine; China National Knowledge Infrastructure; and Wanfang. The following search terms were used: [St John's Wort OR *Hypericum perforatum* OR hypericin OR hyperforin OR johanniskraut (German for St John's wort) OR 圣约翰草 (Chinese for St John's wort)] AND [depression OR antidepressant OR SSRI]. Reference lists of articles also were searched.

Studies were included if the following criteria were met: (1) were randomized controlled trials; (2) compared a standardized extract of SJW with a selective serotonin reuptake inhibitor (SSRI); (3) included patients clinically diagnosed with major depressive disorder according to criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10), or *Chinese Classification of Mental Disorders*, Third Edition (CCMD-3); (4) had extractable outcome measures for treatment efficacy and safety; and (5) included ≥ 20 human subjects. The primary outcome measures were treatment response and safety/incidence of adverse effects (this was evaluated as dropout rate). Treatment response was assessed with (1) the response rate (or relative risk [RR]) ratio of the proportion of responders in the treatment group versus the control group, with response defined as reduction in Hamilton Rating Scale for Depression (HAM-D) score > 50% and (2) remission rate ratio, which is the proportion of remitters in the treatment group versus the control group,

with remission defined as reduction in HAM-D score > 75%. The Jadad scale and the Cochrane Collaboration's tool for assessing risk of bias were used to assess methodology. Heterogeneity was tested statistically, and sensitivity analyses were conducted.

A total of 5428 articles were located and 27 articles met the inclusion criteria. Included studies were from China, Germany, Denmark, Brazil, and the United States. Studies from China had weaker methodological quality and a higher risk of bias, such as inadequate generation of a randomized sequence (selection bias), lack of blinding of outcome assessment (detection bias), and incomplete outcome data (attrition bias). Based on statistical analysis, the likelihood of publication bias was small. The studies included 40 to 428 patients with mild-to-moderate depression. The studies evaluated the following SJW extracts: WS® 5570 (Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany), WS® 5572 (Dr. Willmar Schwabe GmbH & Co. KG), Ze 117 (Zeller AG; Romanshorn, Switzerland), STW3 (Steigerwald Arzneimittelwerk GmbH; Darmstadt, Germany), STW3-VI (Steigerwald Arzneimittelwerk GmbH), LoHyp-57 (Dr Werner Loges and Co., GmbH; Winsen, Germany), and LI-160 (Lichtwer Pharma; Berlin, Germany). They contained standardized 0.3% hypericin and 2-5% hyperforin, with doses of 300-1350 mg/day. The duration of treatment ranged from four to 12 weeks.

According to the meta-analysis, SJW had a similar response rate to SSRIs (pooled RR, 0.983; 95% confidence intervals [CI], 0.924-1.042; P < 0.001). Similar results were found when using a subgroup analysis of only trials with good methodological scores (Jadad scale of 3 or higher). SJW also had similar remission rates to SSRIs (pooled RR, 1.013; 95% CI, 0.892-1.134; P < 0.001). SJW had a significantly lower discontinuation/dropout rate compared to SSRI treatment (pooled odds ratio, 0.587; 95% CI, 0.478-0.697; P < 0.001).

The authors conclude that the "findings further strengthen the support for St John's wort's clinical efficacy in reducing depressive symptoms and more conclusively showed that St John's wort had a significantly smaller number of patients discontinuing treatment/dropping out due to adverse/side effects. This is significant as discontinuation of antidepressants by patients is a common problem faced in the clinical setting, and greatly hampers the success of treatment." The conclusions of this study support the 2008 Cochrane review[1]; however, the present meta-analysis includes more recent studies, larger studies, and studies published in the Chinese literature, thereby extending the findings of the Cochrane review. The authors acknowledge a lack of consensus regarding the appropriate dosage of SJW; however, they did not evaluate the doses used in this meta-analysis. It would have been beneficial if they could have done a sub-analysis to elucidate the optimal dose. Based on the availability of the research, the authors acknowledge that longer-term studies and studies in children < 18 years are needed. This study was very well designed, conducted, and written. It is unique in that it did not exclude non-English articles. The authors report no conflict of interest.

—Heather S. Oliff, PhD

Reference

[1]Linde K, Berner MM, Kriston L. St John's wort for major depression. *Cochrane Database Syst Rev*. October 8, 2008;(4):CD000448. doi: 10.1002/14651858.CD000448.pub3.

The American Botanical Council has chosen not to reprint the original article.