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Review article

Clinical use of *Hypericum perforatum* (St John's wort) in depression: A meta-analysis

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ABSTRACT

Introduction: St John's wort is a popular herbal remedy recommended by Traditional Chinese Medicine (TCM) practitioners and licensed and widely prescribed for depression in many European countries. However, conflicting data regarding its benefits and risks exist, and the last large meta-analysis on St John's wort use for depression was done in 2008, with no updated meta-analysis available.

Methods: Using the keywords [St John's Wort OR *Hypericum perforatum* OR hypericin OR hyperforin OR johanniskraut OR圣约翰草] AND [depression OR antidepressant OR SSRI], a preliminary search (without language restriction) on the PubMed, Ovid, Clinical Trials Register of the Cochrane Collaboration Depression, Anxiety and Neurosis Group, Cochrane Field for Complementary Medicine, China National Knowledge Infrastructure and WanFang database yielded 5428 papers between 1-Jan-1960 and 1-May-2016.

Results: 27 clinical trials with a total of 3808 patients were reviewed, comparing the use of St John's wort and SSRI. In patients with depression, St John's wort demonstrated comparable response (pooled RR 0.983, 95% CI 0.924–1.042, $p < 0.001$) and remission (pooled RR 1.013, 95% CI 0.892–1.134, $p < 0.001$) rate, and significantly lower discontinuation/dropout (pooled OR 0.587, 95% CI 0.478–0.697, $p < 0.001$) rate compared to standard SSRIs. The pooled SMD from baseline HAM-D scores (pooled SMD −0.068, 95% CI −0.127 to 0.021, $p < 0.001$) also support its significant clinical efficacy in ameliorating depressive symptoms.

Limitations: Evidence on the long-term efficacy and safety of St. John's wort is limited as the duration of all available studies ranged from 4 to 12 weeks. It is also unclear if St John's wort would be beneficial for patients with severe depression, high suicidality or suicide risk.

Conclusion: For patients with mild-to-moderate depression, St John's wort has comparable efficacy and safety when compared to SSRIs. Follow-up studies carried out over a longer duration should be planned to ascertain its benefits.

1. Introduction

According to the World Health Organisation (WHO), depression is a common mental disorder with over 350 million sufferers worldwide (Depression Internet, 2016). Currently, depression is the second leading cause of Disability Adjusted Life Years (DALYs) in people aged 15–44 years. By the year 2020, it is expected that depression would be the second leading cause of DALYs for all age groups (Reddy, 2010). Due to its enormous associated disability, depression is a major public health issue with significant direct and indirect health costs (Scott and Dickey, 2003). For example, it is estimated that the National Health Service (NHS) in UK spends more on treating depression than diabetes and hypertension combined (Scott and Dickey, 2003). Additionally, depression accounts for around 60–85% of the cost of illness. This cost is mainly attributed to the amount of productive hours lost that in turn has a substantial drag on a country's Gross National Product (GNP) (Scott and Dickey, 2003).

Therefore, effective management of depression is imperative to reduce the significant morbidity and disability associated with the disease. *Hypericum perforatum* (more commonly known as St John's wort) is an herbaceous perennial plant commonly found in Asia and Europe. It is a popular herbal remedy recommended by TCM practitioners for treating depression (Freeman, 2009). Furthermore, it is licensed and widely prescribed for depression in many European countries. Additionally, St John's wort is also gaining popularity in Western countries, with at least 40% of the sufferers consuming at least

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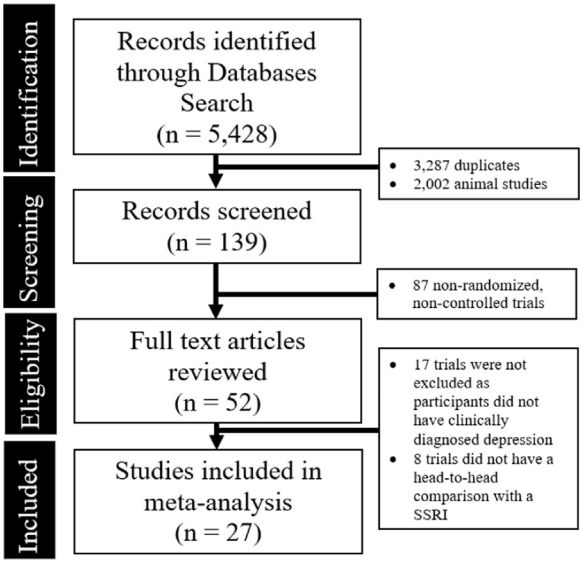

Fig. 1. PRISMA flowchart showing the studies identified during the literature search and abstraction process.

1 TCM in the US annually (Hypericum Depression Trial Study Group, 2002). The burgeoning usage of St John's wort on a global scale warrants accurate information on (1) its efficacy compared to placebo and other conventional antidepressants and (2) its risks-benefits analysis.

However, the literature on St John's wort is rather outdated and conflicting. The last large meta-analysis on the subject was completed in 2008, which showed that the efficacy of St John's wort is superior to placebo and similar to other conventional antidepressants while having less side effects (Linde et al., 2008). However, several other studies have since questioned the efficacy of St John's wort (Hypericum Depression Trial Study Group, 2002; Linde et al., 2005; Freeman et al., 2010). Moreover, while some studies (Linde et al., 2008; Whiskey et al., 2001; Henderson et al., 2002) reported St John's wort to be safer than conventional antidepressants, other studies (Hypericum Depression Trial Study Group, 2002) did not support this conclusion. Therefore, given the outdated and conflicting nature of literature on this issue, this systematic review and meta-analysis is relevant and aims to provide a more updated and clear answer to these questions.

2. Methods

2.1. Patient involvement

This article does not contain any studies with human participants performed by any of the authors. Patients/service users/carers/lay people were not involved in the design or course of this study.

2.2. Search strategy

Literature search was done in accordance with PRISMA guidelines. Using the keywords [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], a preliminary search on the PubMed, Ovid, Clinical Trials Register of the Cochrane Collaboration Depression, Anxiety and Neurosis Group (CCDANTR), Cochrane Field for Complementary Medicine, China National Knowledge Infrastructure (http://www.cnki.net/) and WanFang (http://www.wanfangdata.com/) database yielded 5428 papers published in any language between 1-Jan-1960 and 1-May-2016. Grey literature was not searched. Title/abstract screening were performed independently by the researchers to

Table 1.
Characteristics of all studies included in this review (arranged alphabetically by first Author's last name).

Author, year	Study design	Sample size (N)	St John's wort preparation used	SSRI used	Diagnosis criteria	Depression severity	Outcome measures	Country of origin	Jadad scale
Behnke et al. (2002)	Randomized, controlled trial (RCT)	N=70	Calmigen® (300 mg/d for 6 weeks)	Fluoxetine (40 mg/d for 6 weeks)	ICD–10	Mild to moderate	HAM-D, Clinical Global Impression (CGI)	Denmark	3
Bjerkenstedt et al. (2005)	Randomized, placebo-controlled, multicentre trial	N=174	LI–160 (900 mg/d for 4 weeks)	Fluoxetine (20 mg/d for 4 weeks)	DSM-IV	Mild to moderate	HAM-D, adverse events	Germany	3
Brenner et al. (2000)	Randomized, controlled, double-blind	N=30	LI–160 (600 mg/d for 1 week, then 900 mg/d for 6 weeks)	Sertraline (50 mg/d for 1 week, then 75 mg/d for 6 weeks)	DSM-IV	Mild to moderate	HAM-D, CGI	USA	3
Fava et al. (2005)	Randomized, parallel group, double-blind	N=135	LI–160 (900 mg/d for 12 weeks)	Fluoxetine (20 mg/d for 12 weeks)	DSM-IV	Mild to moderate	HAM-D, CGI, adverse events	Germany	3
Gao (2006)	Controlled, not randomized	N=68	SJW (600 mg/d for 4 weeks)	Paroxetine (20 mg/d for 6 weeks)	Chinese classification of mental disorders (CCMD)–3	HAM-D total score ≥18	HAM-D, Hamilton Anxiety Rating Scale (HAM-A)	China	1
Gastpar et al. (2005)	Randomized, double-blind	N=241	STW3 (612 mg/d for 12 weeks)	Sertraline (50 mg/d for 12 weeks)	ICD–10	Moderate	HAM-D, adverse events	Germany	5
Gastpar et al. (2006)	Randomized, double-blind	N=388	STW3-VI (900 mg/d for 6 weeks)	Citalopram (20 mg/d for 6 weeks)	ICD–10	Moderate	HAM-D, adverse events	Denmark	5
Gu et al. (2001)	Randomized, double-blind	N=135	SJW (900 mg/d for 6 weeks)	Fluoxetine (20 mg/d for 6 weeks)	CCMD–2-R	Mild to moderate	HAM-D, HAM-A, adverse events	China	4
Harrer et al. (1999)	Randomized, double-blind	N=161	LoHyp–57 (800 mg/d for 6 weeks)	Fluoxetine (20 mg/d for 6 weeks)	ICD–10	Mild to moderate	HAM-D, adverse events	Germany	3
Hu et al. (2008)	Randomized, open, controlled	N=70	SJW (900 mg/d for 6 weeks)	Paroxetine (20 mg/d for 6 weeks)	CCMD–3	HAM-D total score ≥18	HAM-D, HAM-A, adverse events	China	2

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