

# Kava and St. John's Wort: Current Evidence for Use in Mood and Anxiety Disorders

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## Abstract

**Background:** Mood and anxiety disorders pose significant health burdens on the community. Kava and St. John's wort (SJW) are the most commonly used herbal medicines in the treatment of anxiety and depressive disorders, respectively.

**Objectives:** The objective of this study was to conduct a comprehensive review of kava and SJW, to review any evidence of efficacy, mode of action, pharmacokinetics, safety and use in major depressive disorder, bipolar disorder, seasonal affective disorder (SAD), generalized anxiety disorder, social phobia (SP), panic disorder (PD), obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD).

**Methods:** A systematic review was conducted using the electronic databases MEDLINE, CINAHL, and The Cochrane Library during late 2008. The search criteria involved mood and anxiety disorder search terms in combination with kava, *Piper methysticum*, kavalactones, St. John's wort, *Hypericum perforatum*, hypericin, and hyperforin. Additional search criteria for safety, pharmacodynamics, and pharmacokinetics were employed. A subsequent forward search was conducted of the papers using Web of Science cited reference search.

**Results:** Current evidence supports the use of SJW in treating mild–moderate depression, and for kava in treatment of generalized anxiety. In respect to the other disorders, only weak preliminary evidence exists for use of SJW in SAD. Currently there is no published human trial on use of kava in affective disorders, or in OCD, PTSD, PD, or SP. These disorders constitute potential applications that warrant exploration.

**Conclusions:** Current evidence for herbal medicines in the treatment of depression and anxiety only supports the use of *Hypericum perforatum* for depression, and *Piper methysticum* for generalized anxiety.

## Introduction

MOOD AND ANXIETY DISORDERS are the most prevalent psychiatric conditions in clinical practice.<sup>1</sup> They often occur comorbidly, and cause significant socioeconomic burden and personal distress.<sup>2</sup> Lifetime prevalences of common disorders are 12%–20% for major depressive disorder (MDD), bipolar disorder 1%–2%, dysthymia 2%–4%, generalized anxiety disorder (GAD) 3%–6%, social phobia (SP) 4%–6%, obsessive-compulsive disorder (OCD) 1%–3%, posttraumatic stress disorder (PTSD) 1%–2%, and panic disorder (PD) 1%–3%.<sup>3,4</sup> These disorders vary depending on country, sex, and method of diagnosis. A constant epidemiological feature is that women have higher rates of MDD and GAD than men.

The pathophysiology of mood disorders is not yet fully understood, with many complex neurological and endocrinological interrelated mechanisms involved.<sup>5</sup> Current evidence suggests that depressive disorders are biologically mediated by a dysfunction of monoamine pathways (e.g.,

receptors and production); secondary messenger system malfunction (e.g., G proteins, cyclic adenosine monophosphate); neuro-endocrinological abnormality (e.g., hyperactivity of the hypothalamic–pituitary–adrenal axis: HPA-axis) and increased serum cortisol, which subsequently reduces brain-derived neurotrophic factor (BDNF) and subsequent neurogenesis.<sup>5,6</sup> Other potential factors include impaired endogenous opioid function, abnormal circadian rhythm, changes in  $\gamma$ -aminobutyric acid (GABA)ergic and/or glutamatergic transmission, and cytokine and steroidal alterations.<sup>5,6</sup>

The biological mechanisms behind bipolar depression and (hypo)mania are purported to involve abnormalities in neural transmission that include the prefrontal, limbic–striatal–thalamic circuits, and anterior cingulate cortices.<sup>7</sup> As in the case of MDD, the serotonergic system and BDNF are important contributors to the pathophysiology of bipolar depression.<sup>8</sup> The pathophysiology behind anxiety disorders is complex and still relatively unknown. Current evidence indicates that the neurobiological influence primarily involves

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dysfunction of GABAergic, glutamatergic, serotonergic, and noradrenergic pathways.<sup>9</sup> Other biologic neuromodulators of anxiety include adenosine, glucocorticoids, cytokines, neuropeptides, and cannabinoids.

Over half of people with severe depression (54%) and anxiety attacks (57%) report using complementary and alternative medicine (CAM) to treat these conditions during the past 12 months.<sup>10</sup> Two thirds of those seen by a conventional provider for MDD also used CAM. Results from a 2001 nationally representative study of 3068 women living in the United States revealed similar use of CAM, with 54% of a subsample of 220 women with depression reporting its use in the previous year.<sup>11</sup>

Kava and St. John's wort (SJW) are the herbal medicines that have been studied most extensively to treat mood and anxiety disorders. A search of the literature on Pubmed for human randomized controlled trials (RCTs) revealed 41 citations for kava and 170 for SJW. In comparison, other traditional herbal medicines used to treat mood and anxiety disorders such as *Passiflora incanata*, *Valeriana* spp. (in depression or anxiety), and *Scutellaria lateriflora* had only six, eight, and one citations, respectively. While good evidence supports the use of kava for generalized anxiety, and SJW for depression, there is an absence of literature reviewing these two prominent phytotherapies for use in other mood and anxiety disorders. To date, there is also no published review that contrasts kava and SJW in depth.

The aim of this review is to explore the current evidence for the use of kava in the main mood and anxiety disorders, and to review efficacy, pharmacodynamics, pharmacokinetics, and safety.

## Methods

The electronic databases MEDLINE (Ovid and Pubmed), CINAHL, and The Cochrane Library were accessed in late 2008. An initial general search was conducted of mood and anxiety disorders. We then further searched these databases using the terms Hypericum perforatum, Piper methysticum, St. John's wort, kava, kavalactones, kavain, hypericin, and hyperforin. We also searched St. John's wort in combination with the search terms Major Depressive Disorder, anxiety, Generalized Anxiety Disorder, dysthymia, bipolar depression, Social Phobia, Panic Disorder, Post Traumatic Stress Disorder, and Obsessive Compulsive Disorder. A forward search of the identified articles was subsequently performed

using Web of Science cited reference search. Meta-analyses and RCTs were primarily reviewed to determine evidence of efficacy. Nonrandomized controlled human trials and animal trials were only reviewed where RCTs were absent. *In vitro* and *in vivo* studies were primarily reviewed to assess pharmacodynamic and pharmacokinetic activity, and to augment existing evidence of activity or safety. Due to the abundance of RCTs located for kava and GAD, and SJW for MDD, we focused on results of meta-analyses and key studies in these cases.

### Piper methysticum (kava)

**Efficacy.** Kava has traditional uses in the South Pacific as a medicine and an inebriant that commonly elicits psychologic and physiologic relaxation.<sup>12</sup> The use of kava traditionally also has cultural significance, being used in rites of passage, funerals, and coronation ceremonies.<sup>12</sup> Recent meta-analyses<sup>13,14</sup> are displayed in Table 1. A Cochrane review has been undertaken of 11 RCTs of rigorous methodology using kava monopreparations (60 mg–280 mg of kavalactones) in *generalized anxiety*.<sup>13</sup> Results revealed statistically significant anxiolytic activity of kava compared with placebo in all but one trial. The meta-analysis of seven trials using the Hamilton Anxiety Scale (HAM-A)<sup>15</sup> demonstrated that kava reduced anxiety significantly over placebo. There was moderate heterogeneity in respect to the type of extract used (acetonic, ethanolic, and standardization), dosage used (60–280 kavalactones), and the sample treated (pre-operative anxiety, climacteric anxiety, state–trait or generalized anxiety disorder diagnoses). The methodological quality of the trials were sound, with four of the seven trials included having the maximum Jadad score<sup>16</sup> of 5. The reviewers should be commended for not including synthetic extracts using L-kavain, as they may not have the same efficacy or safety as whole extracts.

Another meta-analysis based on six placebo-controlled, randomized trials using a standardized kava extract WS1490 in anxiety (assessed via HAMA-A) demonstrated similar findings.<sup>14</sup> The meta-analysis included only WS1490 acetone extracts, and studies of fairly homogenous methodology. Contrary to a supportive conclusion in the abstract, the continuous outcome (a 5.94-point reduction on HAM-A over placebo, 95% confidence interval [CI]: –0.86 to 12.94) was just outside statistical significance ( $p=0.07$ ). When a study by Warneke (1991) was removed, due to an extreme result and

TABLE 1. KAVA REVIEWS, META-ANALYSES, AND STUDIES COMPARING EFFICACY TO SYNTHETICS

Study	Design	Sample size	Results
Pittler et al. 2003	Cochrane Review 11 RCTs	$n = 645$	Significantly greater anxiolysis from Kava than placebo
Pittler et al. 2003	Meta-analysis 6 RCTs HAM-A <sup>a</sup> outcome measure	$n = 345$	HAM-A 5.0-point reduction over placebo (95% CI: 1.1–8.8)
Witte et al. 2005	WS1490 extract 6 RCTs HAM-A outcome measure	$n = 345$	OR = 3.3 (success rate) (95% CI: 2.09–5.22)
Boerner et al. 2003	RCT: 3-arm, 8 weeks kava (400 mg) versus buspirone (10 mg) vs. opipramol (100 mg)	$n = 129$	Equivalent efficacy between treatments on all outcome measures

<sup>a</sup>Primary outcomes on Hamilton Anxiety Scale (HAM-A). RCTs, randomized controlled trials; OR, odds ratio.

restricted sample (women with climacteric syndrome), the result diminished considerably. On the other hand, the review included two studies that used lower kava extract doses, which reduced overall outcomes of the meta-analysis. However, trials of low doses may underestimate potential effects.

Kava has demonstrated equivalent efficacy to synthetic agents in one clinical trial. The study assessed kava in comparison to the synthetic agents buspirone and opipramol in the treatment of GAD.<sup>17</sup> There were no significant differences in efficacy or safety between kava, buspirone, and opipramol. This demonstration of equivocal efficacy is noteworthy, as kava may provide an advantage over benzodiazepines in respect to limiting daytime sedation and cognitive impairment.<sup>18</sup> Preferential use of kava may also have less withdrawal and rebound problems than chronic benzodiazepine use.<sup>19</sup>

Our review revealed no supportive evidence of controlled studies using kava in samples with other specific anxiety disorders such as *SP*, *PD*, *OCD*, or *PTSD*. Kava RCTs such as Volz et al. did incorporate participants with DSM-III-R agoraphobia, specific phobia, and adjustment disorder with anxiety in their sample, in addition to people with GAD.<sup>20</sup> The 25-week multicenter RCT using a standardized extract demonstrated a significant superiority on the HAM-A after 8 weeks of administration.

Our review of the literature revealed no published study on kava monotherapy for any *depressive disorder*. While Commission E recommends against prescribing kava in cases of depression, it appears that no human data currently support that position.<sup>21</sup>

**Pharmacodynamics and pharmacokinetics.** The pharmacodynamic mechanism for kava's anxiolytic action has not yet been clearly elucidated. Conflicting evidence exists regarding modulation of GABA receptors that are mainly responsible for anxiolysis. Although a previous study showed an increased synergistic effect of [3H]muscimol binding to GABA- $\alpha$  receptors by kavalactones,<sup>22</sup> other studies specifically evaluating direct kavalactone binding to GABA receptors have not supported this activity.<sup>23,24</sup> Current evidence indicates that kavalactones modulate GABA activity via alteration of lipid membrane structure and sodium channel function, rather than by significant GABA- $\alpha_{1,2}$  agonism.<sup>25,26</sup> Importantly, animal models have shown this activity to occur in the hippocampus and amygdala (the primary biologic loci of anxiety).

A downregulation of  $\beta$ -adrenergic activity is another possible pharmacodynamic mechanism for anxiolysis.<sup>27</sup> Monoamine oxidase (MAO)-B inhibition may also provide an anxiety-reducing effect as revealed via *in vitro* studies.<sup>28</sup> Kavalactones do not appear to modulate serotonergic pathways (i.e., binding to these receptors or influencing re-uptake).<sup>29</sup> Kavalactones have demonstrated relaxation of muscular contractibility, as assessed via *in vitro* and *in vivo* examinations.<sup>30,31</sup> As somatic tension is a common manifestation of anxiety disorders,<sup>32</sup> and subjective anxiety is partly judged by an awareness of tension and arousal, this action may have beneficial effect. A novel pharmacological activity of kava that distinguishes it from synthetic anxiolytics is its ability to inhibit re-uptake of noradrenaline. This action (demonstrated in animal models) may be responsible for kava's effect of improving concentration.<sup>18,29</sup>

An issue of importance is the use of isolated kavalactones in many studies, rather than the whole kava extract. Because synergy is a well-established component of herbal efficacy, this method may obscure the full pharmacologic impact of the plant. An example is dopamine modulation by individual kavalactones. An *In vitro* assay revealed that the kavalactone yangonin decreased dopamine levels, while kavalactone demethoxy-yangonin increased the monoamine.<sup>33</sup>

In respect to the hepatic pharmacokinetic modulation of cytochrome P450 involving kava or the individual kavalactones, animal and *in vitro* models have revealed differing results. Pharmacokinetic studies conducted by Mathews and colleagues<sup>34,35</sup> using whole kava extracts and individual kavalactones in human hepatic microsomal P450s revealed significant inhibition of the activities of CYP1A2 (56% inhibition), 2C9 (92%), 2C19 (86%), 2D6 (73%), 3A4 (78%), and 4A9/11 (65%). The kavalactones dihydromethysticin, desmethoxy-yangonin, and methysiticin were found to be the most potent inhibitors. The group's 2005 study demonstrated similar results, and additionally revealed that a whole kava extract did not induce P-glycoprotein (Pgp) activity compared to control. Other assays have also demonstrated that kava inhibits CYP3A4,<sup>36</sup> while an induction of CYP3A23 occurred with dihydromethysticin and desmethoxy-yangonin in an animal model.<sup>37</sup> The synergistic interactions between kavalactones support the idea that therapeutic effects of whole kava extracts or combinations of the main six kavalactones (comprising 96% of the total kavalactones) are likely to be different from those of single kavalactones. To this end, there is a deficit of human studies examining the pharmacokinetics of kava. A human pharmacokinetic trial ( $n=12$ ) using probe drug cocktails of midazolam and caffeine, followed 24 hours later by chlorzoxazone and debrisoquin, demonstrated CYP2E1 inhibition of approximately 40%.<sup>38</sup> In respect to absorption, excretion, and disposition, an animal model has shown that kavain is rapidly absorbed, and is excreted mainly via urine.<sup>34</sup> Approximately 90% of kavain is excreted 72 hours after administration, with about 0.4% being retained in the tissues (with no propensity to accumulate in any particular tissue).

Although the potential of kava-drug interactions should be considered, unlike SJW, to our knowledge no adverse events due to pharmacokinetic interaction with pharmaceutical medicines have been documented. This may be due to a lack of Pgp induction by kava. Because of the inhibitory effect of kava on a range of cytochrome (CYP) P450s (discussed below), potential drug toxicities may occur from high serum drug levels, especially in preparations with narrow therapeutic extracts.

The two most commonly held concerns regarding potential interaction of the herb with benzodiazepines or alcohol still has not been sufficiently studied. A theoretical concern with benzodiazepines is synergistic sedation,<sup>39</sup> although no clinical evidence currently supports this hypothesis. One study in humans demonstrated that alcohol co-administration with kava causes increased sedation and a deleterious effect on cognitive and visuomotor functions.<sup>40</sup> It should be noted that alcohol metabolism appears to be unaffected by kavalactones, with no inhibition of alcohol dehydrogenase occurring in an *in vitro* assay.<sup>41</sup> However, concerns over hepatotoxicity support advice to minimize or avoid use of alcohol while taking kava.

**Safety.** Kava is currently restricted from use in the United Kingdom, Canada, and the European Union, primarily due to concerns over hepatotoxicity.<sup>42</sup> At least 93 cases of hepatotoxicity have been documented wherein kava may be implicated.<sup>42</sup> Most cases were poorly reported and many involved the concurrent ingestion of pharmaceuticals and alcohol, excessive daily dosage or long-term administration, and also may have involved preparations that used inappropriate kava cultivars, or aerial or root peelings that are higher in alkaloids.<sup>42,43</sup> Previous hepatotoxicity caused by European kava products may in part be due to a commercial cost-motivated preference for the aerial parts and root or stem peelings that contain the alkaloid pipermethystine, and due to the use of nontraditional solvents (ethanol and acetone). There are various possible causes of hepatotoxicity from kava: These involve the inhibition of CYP P450 (perhaps especially in the presence of a genetic insufficiency of CYP P450 2D6), reduction of liver glutathione content (or other enzymes needed to metabolize kavalactones), and inhibition of cyclo-oxygenase enzyme activity.<sup>44,45</sup> Data from short-term postmarketing surveillance studies and clinical trials report no cases of hepatotoxicity, and demonstrate that adverse events are rare, mild, and reversible.<sup>46</sup>

A report commissioned by the World Health Organization (WHO) assessing the risk of kava products<sup>42</sup> suggested that products from water-based suspensions should be developed and tested in clinical trials, and that these preparations should preferentially be used over acetone and ethanol extracts. A recent *in vitro* study using methanolic and acetonic root, and methanolic leaf extract showed cytotoxicity in liver mitochondria starting at a concentration of 50 µg/mL.<sup>47</sup> However, *in vitro* assays using aqueous extracts revealed no hepatotoxicity.<sup>48</sup> On the other hand, *in vivo* animal models have revealed no liver toxicity from nonaqueous extracts,<sup>49</sup> and 2 cases of human hepatotoxicity in New Caledonia have occurred from aqueous extracts.<sup>50</sup>

The WHO (2007) review of case reports of hepatotoxicity stated that in only 3 cases could firm causality be established.<sup>42</sup> In other cases, poor reporting of dosage, frequency, use of concomitant medication or alcohol, and of any existing hepatic problems made the report difficult to interpret. The author noted that in many cases, a differential diagnosis of viral hepatitis was also possible, although in all cases of liver transplants the histology was negative. In 5 cases, dechallenge and re-challenge were undertaken, and all had the liver problems re-occur upon re-challenge, although only in 1 case was kava coded as the "probable" causation. Hepatotoxicity has occurred in people taking acetonic, ethanolic, synthetic, and water preparations, but synthetics show a relative risk of 6.31 (95% CI: 1.80–22.15), while acetone or ethanol extracts have a relative risk of 7.09 (95% CI: 2.15–23.37). No significant difference was found between ethanol and acetone extracts.

Traditional knowledge suggests that liver toxicity is not associated with kava use, with Fijian kava-users typically consuming over 100,000 bowls in a lifetime.<sup>42</sup> Still, studies of traditional recreational use of the plant indicate that liver function parameters can be altered with moderate use. A study of 31 healthy adult kava drinkers from Tonga revealed that chronic kava beverage consumption was associated with an elevation of  $\gamma$ -glutamyl-transferase (GGT) liver enzyme in 65% of the kava drinkers, versus 26% in controls ( $n = 31$ ).<sup>51</sup>

The alkaline phosphatase (ALP) liver enzyme was also elevated in 23% of kava drinkers versus 3% in the controls. Although the study controlled for concomitant alcohol consumption, the sample was not balanced between genders, with the active group comprising 90% males compared with a mainly female control group (81%). A study of kava use (average 118 g/week) in an Arnhem Land community in the Northern Territory of Australia<sup>52</sup> found that 340 users who consumed kava within the previous 24 hours displayed higher GGT levels than nonusers did. Higher ALP levels also occurred in those who last used kava within the previous 2 weeks. This effect appears to be reversible, with liver enzymes returning to baseline after 1 to 2 weeks' abstinence from kava. Because no evidence of irreversible liver damage has been found in studies of traditional kava use, GGT and ALT modulation most likely reflects metabolic-induced enzyme induction, rather than the changes in liver function reflecting inflammation or cell death.

As discussed above, kava has been observed to cause concentration-dependent decreases in CYP 450 activities, thereby holding the potential for drug interactions. Our review revealed no human data assessing this risk. Pharmacokinetic studies, case report analyses, and cohort studies on this issue are urgently required. At present, the benefit-to-risk ratio of kava is highly favorable, with good clinical efficacy and a low risk of adverse reactions. Because current synthetic pharmacological treatment with benzodiazepines has greater potential health risks and dependency issues, kava remains a viable therapeutic option.

To address safety issues, kava could be removed from "over the counter" public use, being prescribed by health-care professionals only. The short-term or intermittent use of aqueous root preparations standardized for kavalactones (at daily doses of < 250 mg kavalactones), and the avoidance of concomitant use with alcohol or in cases of known hepatic insufficiency or disease should also be observed.

### *Hypericum perforatum* (SJW)

**Efficacy.** The flowering tops of *H. perforatum* (SJW) of the Clusiaceae family is used extensively in Europe as an antidepressant agent. In Germany, SJW is one of the most prescribed antidepressant agents, with more than 100 million daily doses.<sup>53</sup> Since 2000, four primary meta-analyses of SJW on depression have been conducted,<sup>54–57</sup> using the Hamilton Depression Scale (HAM-D)<sup>58</sup> as the outcome measure (Table 2).

As can be seen in Table 2, reviews on SJW have consistently found that it produces a significantly greater impact on HAM-D Depression than placebo. Positive responses to SJW (i.e.,  $\geq 50\%$  reduction on HAM-D) ranged from 46.8% to 60.8% in different comparison categories or trial sets. Reviews found that effects of SJW were somewhat greater in older or smaller trials. Our review of the literature concluded that this is conceivably due to older trials having a lesser placebo response, and the quality of the study designs becoming more rigorous. However, funnel-plot analyses in the reviews did not suggest that results were substantially affected by publication biases. The latest Cochrane review (2008) updated from 2005 revealed similar data to the previous review after inclusion of further studies comparing selective serotonin reuptake inhibitors (SSRIs) to SJW ex-

TABLE 2. ST. JOHN'S WORT (SJW) REVIEWS AND META-ANALYSES OF RANDOMIZED CLINICAL TRIALS USING THE HAMILTON RATING SCALE FOR DEPRESSION (HAM-D) AS THE OUTCOME MEASURE

Study	n of trials	Participants		RR (95% CI) <sup>b</sup>	Mean response <sup>a</sup>	
		SJW	Comparison		SJW	Comparison
<b>SJW versus placebo</b>						
Linde et al. (2008)	9 larger	1129	915	1.28 (1.10–1.49)	56.7%	43.6%
	9 smaller	506	514	1.87 (1.22–2.87)	46.8%	23.2%
Röder et al. (2004)	18	1086	1043	1.52 (1.28–1.75) <sup>c</sup>	53.3%	32.7%
Werneke et al. (2004)	18	*	*	1.73 (1.40–2.14)	*	*
Whiskey et al. (2001)	14	690	646	1.98 (1.49–2.62)	56.5%	28.5%
<b>SJW versus synthetic antidepressants</b>						
Linde et al. (2008)	SSRIs	12	905	1.00 (0.90–1.15)	52.0%	52.0%
	Tri/tetracyclic	5	508	1.02 (0.90–1.15)	48.6%	48.8%
Röder et al. (2004)		15	1117	1.04 (0.93–1.78) <sup>c</sup>	53.2%	51.3%
Whiskey et al. (2001)		9	694	1.00 (0.90–1.11)	60.8%	60.4%

<sup>a</sup>Response  $\geq 50\%$  reduction on HAM-D.

<sup>b</sup>Higher values represent a superiority from SJW.

<sup>c</sup>The original article reported the reciprocal ratio.

\*Data not provided in the review.

SSRIs, selective serotonin reuptake inhibitors; RR, relative risk; CI, confidence interval.

tracts. Results still revealed equivalent efficacy between the comparators.

SJW has now demonstrated similar or greater efficacy to synthetic antidepressants. Rigorous RCTs have evaluated SJW against placebo and fluoxetine in treating MDD, with outcomes being commonly assessed via HAM-D and Clinical Global Impression (CGI).<sup>59</sup> Four (4) studies demonstrated that SJW had similar<sup>60,61</sup> or superior<sup>62,63</sup> effects to those of fluoxetine. SJW also appears to have similar antidepressant effects as imipramine,<sup>64–67</sup> citalopram,<sup>68</sup> maprotiline,<sup>69</sup> and amitriptyline.<sup>70</sup> In comparison with paroxetine, SJW was statistically more effective in treating moderate to severe depression.<sup>71</sup> When trialed against sertraline, SJW had comparable efficacy in four RCTs, as measured via HAM-D, the Beck Depression Inventory,<sup>72</sup> and CGI scales.<sup>73–76</sup>

There is ongoing debate about the use of SJW for treating moderate to severe depression. Arguments against this use are often based on the 2002 Hypericum Depression Trial Study Group (2002) research, which revealed that SJW was no more effective than placebo.<sup>73</sup> What is commonly omitted in discussion of this trial is that it also found that sertraline also had effects comparable to those of placebo on the primary outcome measures. In contrast, a 6-week 2005 RCT ( $n=251$ ) comparing SJW extract WS 5570 (900 mg/day), paroxetine (20 mg/day), and placebo in moderate to severe depression (HAM-D  $\geq 22$ ), demonstrated that SJW had therapeutic superiority to paroxetine (HAM-D reduction  $-14.4$  ( $\pm 8.8$ ) on SJW, versus  $-11.4$  [ $\pm 8.6$ ] for paroxetine).<sup>71</sup> Although SJW is commonly now only recommended for mild to moderate depression,<sup>73,77,78</sup> we found no definitive evidence to preclude its use in more severe conditions, and the herb may still have a role in nonresponders to synthetic antidepressants.

Despite meta-analyses and risk-benefit profiles advocating the use of SJW in mild-to-moderate depression, there is still some resistance to its prescription by medical practitioners. A random sample of 350 medical practitioners in Australia were assessed via a postal questionnaire survey to determine their knowledge and recommendation of SJW,<sup>79</sup> and 48% (153/319)

responded. Only 31% reported recommending SJW to patients, and only a third provided specific dosage instructions. Knowledge of potential side-effects and drug interactions of SJW by medical practitioners was poor, in comparison with their knowledge of synthetic antidepressants.

In other depressive disorders, evidence of efficacy is sparse. Only one study on *dysthymia* was located. A RCT involving 150 participants with depression and dysthymia, using a standardized SJW extract PM235 (810 mg/day), observed that while improvement occurred in nondysthymic patients, no statistical improvement was revealed in International Classification of Diseases-10 diagnosed dysthymic patients on several outcome measures such as HAM-D.<sup>80</sup> In respect to seasonal affective disorder, the evidence is tentatively supportive. Two (2) open-label trials using SJW alone and SJW plus light therapy found there was significant reduction of winter-provoked depression compared to placebo, while there was no statistical difference between the two active treatments.<sup>81,82</sup> One (1) RCT was identified using SJW in SP. A placebo-controlled pilot study using SJW (flexible-dose 600–1800 mg daily) for 20 people with SP found no significant differential impact over placebo on the Liebowitz Social Anxiety Scale, although a trend toward improvement was demonstrated.<sup>83</sup> An initial study using SJW for the treatment of OCD was encouraging. The 12-week open-label exploratory study using SJW (900 mg per day) demonstrated a significant change of 7.4 points on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).<sup>84,85</sup> A recent controlled study, however, did not replicate the previous findings.<sup>86</sup> The 12-week RCT using a standardized SJW (LI 160) extract at a flexible dose of 600–1800 mg/day or placebo administered to 60 adults did not ameliorate OCD on the Y-BOCS ( $-3.43$ ) in comparison with placebo ( $-3.60$ ), or differentially affect clinician ratings.

When reviewing the dosages in these studies, it should be noted that most clinical evidence is based on extracts that are standardized and concentrated. This may not reflect all SJW prescriptions used in clinical practice, where some hydroalcoholic extracts result in a lower effective dose.

TABLE 3. KAVA AND ST. JOHN'S WORT CONTRASTED

	Mechanism of action	Cautions and Contraindications
Kava ( <i>Piper methysticum</i> )	<ul style="list-style-type: none"> <li>■ GABA membrane modulation</li> <li>■ Weak GABA binding</li> <li>■ Blockage of voltage-gated channels</li> <li>■ <math>\beta</math>-adrenergic downregulation</li> <li>■ MAO-B inhibition</li> </ul>	<ul style="list-style-type: none"> <li>■ In known hepatotoxicity</li> <li>■ With alcohol, anticonvulsants, or benzodiazepines</li> <li>■ In unipolar "nonanxious" major depressive disorder</li> </ul>
St. John's wort ( <i>Hypericum perforatum</i> )	<ul style="list-style-type: none"> <li>■ Nonselective inhibition of re-uptake of serotonin, dopamine, norepinephrine</li> <li>■ <math>\downarrow</math> Degradation of neurochemicals</li> <li>■ <math>\uparrow</math> Sensitization and <math>\downarrow</math> binding to various neuroreceptors</li> <li>■ <math>\uparrow</math> Dopaminergic activity (prefrontal cortex)</li> <li>■ Cortisol/HPA-axis modulation</li> </ul>	<ul style="list-style-type: none"> <li>■ Co-administration with synthetic antidepressants</li> <li>■ Hyperforin-rich extracts with medications (e.g., OCP)</li> <li>■ In bipolar depression</li> </ul>

Primary references:<sup>42,99</sup>

GABA,  $\gamma$ -aminobutyric acid; MAO-B, monoamine oxidase-B; OCP, oral contraceptive pills; HPA, hypothalamic-pituitary-adrenal.

**Pharmacodynamics and pharmacokinetics.** The mechanism of antidepressant action of SJW has not been fully elucidated to date, and is currently posited to involve the modulation of various neurochemical pathways<sup>87</sup> (see Table 3 for summary). *In vitro* experiments suggest that MAO oxidase inhibition by SJW is weak, and that this is not the main mechanism of antidepressant action.<sup>88,89</sup> Nonselective inhibition of the neuronal re-uptake of serotonin, dopamine, and norepinephrine has been documented via *in vitro* and *in vivo* studies.<sup>90</sup> This activity is likely to occur in part via modulation of Na<sup>+</sup> gradient membranes, with SJW causing sodium influx into the neuron, which then leads to the release of intracellular calcium; this results in increased cell membrane fluidity and communication.<sup>91,92</sup> A decreased degradation of neurochemicals, and a sensitization of and increased binding to various receptors (e.g., GABA, glutamate, and adenosine) have been observed.<sup>87,93,94</sup> In addition, increased dopaminergic activity in the prefrontal cortex has also been documented.<sup>95</sup> A precaution in extrapolating these results to human pharmacodynamics is that intraperitoneal (rather than oral) administration is often used, and little research has involved human studies.

In the last 2 decades, cortisol has achieved increased attention in the study of the pathogenesis of depression. Substantial evidence exists for the role of cortisol and the HPA axis in depression.<sup>96</sup> *In vitro* and animal models have demonstrated that HPA-axis dysfunction and increased cortisol attenuate the production of BDNF in the brain.<sup>6,96</sup> Synthetic antidepressants appear to regulate the HPA axis and increase the production of BDNF.<sup>96</sup> Human studies have found that SJW modulates salivary and serum cortisol levels.<sup>97,98</sup> In animal models, hypericin and the flavonoid derivatives have been demonstrated to downregulate plasma ACTH and corticosterone levels after 2 weeks of daily treatment.<sup>99</sup>

Of the 50%–70% of currently identified constituents, hyperforin, hypericin, and various flavonoids appear to be responsible for the neurochemical modulation.<sup>99</sup> Hyperforin is a lipid-soluble, bicyclic, prenylated phloroglucinol derivative that was first isolated in 1975 by Bystrov and co-workers.<sup>100</sup> *In vitro* and animal models have revealed that hyperforin consistently displays the most neurologically relevant antidepressant activity in comparison to hypericin and flavonoid constituents. Several pharmacological models (e.g., learned helplessness, elevated plus maze, passive avoidance, and

scopolamine and reserpine depression tests) have shown that hyperforin-free preparations were not effective. A controlled human clinical trial ( $n = 147$ ) showed greater efficacy for the 5% hyperforin standardized SJW over the 0.5% extract.<sup>101</sup> The 5% hyperforin extract significantly reduced HAM-D depression, whereas the 0.5% hyperforin extract was not more effective than placebo after 6 weeks of treatment. A quantitative topographic electroencephalogram (qEEG) study of SJW in healthy volunteers biologically reflects this activity. A 5.0% hyperforin formulation produced higher increases in qEEG  $\delta$ - and  $\beta$ -1 frequency values, with a trend in the  $\theta$ - and  $\alpha$ -1 frequency baseline power performances, in comparison with placebo or a 0.5% hyperforin standardized extract.<sup>102</sup> Another supportive argument regarding the use of hyperforin-enriched extracts is that hyperforin crosses the blood-brain barrier, whereas hypericin does not.

In respect to pharmacokinetics, plasma concentrations of hyperforin from a standardized oral preparation (WS 5572: standardized to 5% hyperforin) reached a maximum level after 3.5 hours in human volunteers, with a half-life of 3 hours, and an elimination time of 9 hours.<sup>53</sup> Hypericin is a naphthodianthrone compound that yields red pigment in extracts. The human pharmacokinetics of hypericin have been studied in several *in vivo* trials. The half-life of hypericin has been documented as approximately 21 hours, with the peak serum level occurring after approximately 6 hours.<sup>53,103</sup> The flavonoid glycosides of SJW represent up to 4% of the secondary metabolites.<sup>99</sup> The pharmacokinetics of different flavonoid compounds vary, with half-lives ranging from 1 to 9 hours.<sup>53,103</sup>

**Safety.** A study of prescription drug-related mortality, using U.S. death certificate data, discovered that death occurring from antidepressant medication (excluding tricyclics) rose by 130% (687 to 1582 deaths) from the years 1999 to 2003 (due in part to increased use).<sup>104</sup> The safety profile of SJW in comparison is sound, with a systematic review detailing that the degree of adverse effects in 35,562 pooled patients was 0%–5.7%.<sup>105</sup> The low incidence in the rate of SJW adverse events compares favorably with synthetic antidepressants. A meta-analysis of tricyclic antidepressants ( $n = 1270$  participants) and SSRIs ( $n = 1149$ ) showed an adverse events rate leading to withdrawal of 14.4% (versus 5.2 on placebo) and

5.4% (versus 2.6% on placebo), respectively.<sup>106</sup> Adverse effects leading to dropout in clinical trials were analyzed in the recent SJW Cochrane review (2008). There were significantly more withdrawals due to adverse effects of tri/tetracyclic antidepressants (9.8%) than with SJW (2.4%; odds ratio = 0.24; 95% CI: 0.13–0.46), and from SSRI antidepressants (6.8%) than SJW (3.6%; odds ratio = 0.53; 95% CI: 0.34–0.83).

A review of 16 postmarketing surveillance studies of SJW ( $n = 34,834$ )<sup>107</sup> revealed that the herbal medicine was 10-fold safer than synthetic antidepressants (adverse effects: 0.1%–2.4%). Aside from rare idiosyncratic reactions, most adverse effects involve reversible dermatological and gastrointestinal symptoms. Several case reports have reported possible SJW-induced mania, psychosis, and serotonin syndrome.<sup>105,108</sup> In 12 cases, the diagnosis was mania or hypomania. Causality between SJW and psychosis was not definitive, because re-challenges and de-challenges were not undertaken. These case studies typically also have concomitant use of other medications and/or recreational drugs, and a background of cyclothymia.<sup>109–111</sup> However, in several cases a clear chronological association appeared to exist between SJW use and induction of hypomania or mania, so caution is warranted in people with a personal or family history of bipolar depression. It should also be noted that these concerns are also extended to synthetic antidepressants. Several case reports of serotonin syndrome have been documented by drug surveillance agencies.<sup>105</sup> Currently, however the specificities of this interaction are only based on a theoretical hyperserotonergic effect. Considering the millions of daily doses of SJW taken by consumers worldwide, these reactions (although probably under-reported) appear to be extremely rare.

Dependency or abuse of SJW has never been established. Although isolated hyperforin and hyperforin-rich extracts have been shown to increase dopamine levels and dopaminergic transmission in the prefrontal cortex and *substantia nigra* of rats (pleasure/addiction pathways)<sup>112</sup> in normal therapeutic oral doses of SJW, this effect has not been established and is highly unlikely. One case of misuse and overdose has been documented in Australia.<sup>113</sup> A 16-year-old girl presented to an emergency department with seizures and confusion. She had been taking up to 15 tablets of SJW a day during the 2 weeks prior to being admitted, and had acutely consumed 50 tablets of SJW. A provisional diagnosis of seizures due to overdose of SJW was made. Her health returned to normal within 2 days, and she was discharged on day 6 with no following seizures occurring in the subsequent 6 months.

Certain SJW preparations have been documented to reduce the serum levels of many pharmaceuticals. Two major pharmacokinetic effects appear to be responsible for this, namely, an upregulation of intestinal Pgp and the induction of CYP P450 3A4. Current evidence suggests that this is due to hyperforin increasing the expression of the pregnane X receptor, which increases Pgp expression, as well as inducing CYP 450 3A4 activity.<sup>114–118</sup> CYP P450 enzymes metabolize a wide range of drugs, including hormone-based preparations (e.g., oral contraceptive pills), benzodiazepines, antidepressants, anticoagulants, and antibiotics.<sup>117</sup>

A systematic review was conducted to investigate the effect of SJW extracts on the metabolism of drugs by CYP3A.<sup>117</sup> All of the 19 studies that used high-dose hyperforin extracts (>10 mg/day) had outcomes consistent with CYP3A induction, while the three studies using low-dose hyperforin ex-

tracts (<4 mg/day) demonstrated no significant effect on CYP3A.

Extrapolation of pharmacokinetic activity from studies using hyperforin-rich preparations may not reflect the effect of low hyperforin preparations, and hence may not affect CYP3A and Pgp induction.<sup>115,118</sup> The importance of hyperforin for clinical efficacy may be overvalued; the inclusion of hyperforin at higher levels ultimately negatively affected the risk–benefit ratio (i.e., more drug interactions with no increase in efficacy). On the other hand, as detailed above, hyperforin-enriched extracts frequently display more antidepressant activity.

## Conclusions

Overall, the risk–benefit profile of SJW supports its confident recommendation as a first-line treatment of mild-to-moderate depression. As yet, there is little evidence for its use in other mood disorders. In respect to hyperforin-enriched or hyperforin-free SJW extracts, there are pros and cons for both formulations. A balance could be for hyperforin-rich extracts to be available to be prescribed in people who are not concurrently taking any medication (higher hyperforin may improve efficacy). In cases of people currently or planning on co-medicating, a low hyperforin or hyperforin-free extract should be prescribed to minimize potential drug interactions. Kava had greatest evidence of efficacy for treatment of generalized anxiety. Surprisingly, there are few trials of kava for anxiety disorders other than GAD, and in particular, RCTs on SP, OCD, PTSD, and PD are required. In addition, human pharmacokinetic studies are urgently needed, as are studies of potential interactions between kava and other drugs.

## Disclosure Statement

The contributors declare no completing interests.

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