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Herbal medicines in the treatment of psychiatric disorders: 10-year updated review

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This paper provides a 10-year update of the 2007 systematic review of herbal medicines studied in a broad range of psychiatric disorders, including depression, anxiety, obsessive–compulsive, seasonal affective, bipolar, psychotic, phobic, somatoform, and attention-deficit hyperactivity disorders. Ovid Medline, PubMed, and the Cochrane Library were searched for herbal medicines with both pharmacological and clinical evidence of psychotropic activity. This updated review now covers clinical trial evidence for 24 herbal medicines in 11 psychiatric disorders. High-quality evidence was found to exist for the use of *Piper methysticum* (Kava), *Passiflora spp.* (passionflower) and *Galphimia glauca* (galphimia) for anxiety disorders; and *Hypericum perforatum* (St John's wort) and *Crocus sativus* (saffron) for major depressive disorder. Other encouraging herbal medicines with preliminary evidence include *Curcuma longa* (turmeric) in depression, *Withania somnifera* (ashwagandha) in affective disorders, and *Ginkgo biloba* (ginkgo) as an adjunctive treatment in Schizophrenia. Although depression and anxiety are commonly researched, many other mental disorders still require further prospective investigation. Although the previous review suggested increasing the adjunctive study of select herbal medicines with pharmaceuticals, this was still only found to sparingly occur in research designs. Aside from this, future focus should involve the incorporation of more biomarker analysis, in particular pharmacogenomics, to determine genetic factors moderating response to herbal medicines.

KEYWORDS

anxiety, clinical trials, depression, herbal medicine, medicinal plants, mood disorders, psychiatric disorders, psychiatry

1 | INTRODUCTION

The role of herbal medicine in the treatment of various psychiatric disorders has become more established over the past decade, with phytotherapeutic preparations such as *Hypericum perforatum* (St John's wort) and *Piper methysticum* (Kava) possessing respectable clinical evidence. In 2007, due to the previous deficit of broad and comprehensive reviews (aside from the light review by Wong, Smith, & Boon, 1998), a systematic review of herbal medicines across a breadth of psychiatric disorders was conducted (Sarris, 2007). Twenty-seven plant medicines were originally reviewed in 2007 using a rudimentary systematic literature search used to identify relevant trials of herbal medicines in the treatment of major psychiatric disorders. A summary of that review revealed that a range of plant medicines indicated potential efficacy; however, aside from Kava and St John's wort, many of these medicines featured only in isolated small sample studies.

The purpose of this narrative systematic review is to provide a 10-year update of the research in the field and to investigate and detail further research that has been conducted. This review employs a tightened and more targeted inclusion criteria in order to succinctly synthesize the evidence and to provide more room to discuss any key developments in the field and areas still needing research attention. This update is also of importance given the revision of the Diagnostic and Statistical Manual for Psychiatric Disorders to Edition 5 (APA, 2013).

2 | METHODS

The specific focus of this review was to locate human studies involving herbal medicines for the treatment of major psychiatric disorders or mental health symptoms (secondary mental health outcome data from nonpsychiatric disorder studies were omitted). To this end, the

electronic databases Ovid Medline, PubMed, and The Cochrane Library were originally accessed in early 2007; with an updated search occurring during September to October 2017. Ovid Medline was searched using the search term "Herb$" and the subheadings "Plants, Medicinal," "Plant Extracts," "Phytotherapy," "Plant Preparations" in combination with the search terms "Depress$," "Major Depressive Disorder," "Anxiety," "Generalized Anxiety Disorder," "Dysthym$," "Seasonal Affective Disorder," "Bipolar Disorder," "Panic Disorder," "Phobi $," "Obsessive Compulsive Disorder," "Somatoform Disorder," "Schizophrenia," and "Psychotic Disorder." PubMed and Cochrane databases were accessed, with MeSH being employed to search major psychiatric topics "Depressive Disorder," "Depression," "Dysthymic disorder," "Bipolar Disorder," "Anxiety," "Anxiety Disorders," "Phobic Disorders," "Panic Disorder," "Seasonal Affective Disorder," "Somatoform Disorders," "Psychotic Disorders," "Schizophrenia," Attention Deficit Hyperactivity Disorder, in combination with the MeSH terms, "Plants," "Medicinal," "Plant extracts," "Phytotherapy." A forward search of the papers reviewed was subsequently performed using Web of Science cited reference search. Herbal medicines with known traditional or modern usage were also individually reviewed in PubMed and Ovid databases by conducting a search using the name of the herbal medicines, for example, "St John's wort" or "Hypericum."

An assessment based on the hierarchy of evidence was undertaken, with meta-analyses and randomized controlled human clinical trials (RCTs) reviewed where possible (Altman et al., 2001; Gagnier et al., 2006). Nonrandomized- or nonplacebo-controlled human trials were reviewed where there was also preclinical data. In vitro studies were only reviewed to assess safety data, constituents responsible for activity, or to further determine use. A primary focus was on evidence concerning whole herbal extracts (rather than isolated constituents) as this use occurs in standard phytotherapeutic practice. Studies using intravenous, topical, or inhalant administration were excluded, as these methods do not reflect oral pharmacokinetics and subsequent pharmacodynamic activity that occur from per os delivery in humans.

The major change in this updated review is that traditional Chinese or Kampo formulas found in the original search (Xiaoyao, Gan Mai Da Zao, Chaihu-Shugan-San, Shuganjieyum Ganmia Dazao, Gamisoyo-San, Yokukasan, Wuling, Saiboku-to, Sho-ju-sen, Suanzaorentang, Ting-chih-wan, and Banxia houpu) were not detailed in this review, as the literature has increased markedly in the past decade in this area, and a separate systematic review of these formulas is advised. Studies involving targeted combinations of herbal medicine, for example, Valerian and Kava for anxiety, were however included. Studies on isolated constituents were not included unless when referencing understanding of the active constituents (and aside from curcumin, which is considered to be the primary active constituent of turmeric [a similar position could be taken regarding Milk Thistle research when assessing studies using silymarin]). Due to this, certain plant medicines and formulas were removed from this update, in addition to the mention of *Echium anoemun* (Borage) due to safety concerns.

Studies detailing secondary analyses of the primary data were not included due to word limits. A new section on attention deficit hyperactivity disorder (ADHD) is also added; however, developmental, cognitive/neurological (unless within a psychiatric disorder), sleep, eating, substance-abuse disorders, and menstrual dysphoria were still excluded from the review due to manuscript size constraints. The final change was truncation in the introductory sections of the disorder descriptors (e.g., diagnosis, prevalence, and cost) in order to provide more space for discussion of the herbal medicine literature. For ease of reading, the raw statistics are omitted, with "significant" effects reflecting a *p* value of <.05.

3 | OVERVIEW OF THE DATA

The updated review revealed 24 individual herbal medicines being used for 11 psychiatric conditions (see Tables 1 and 2, respectively, for the list of psychiatric conditions and herbal medicines reviewed (cf. Sarris, Panossian, Schweitzer, Stough, & Scholey, 2011 for a table summarizing constituents and psychopharmacology). Meta-analyses were available for three herbal medicines (*Crocus sativus* [saffron]; St John's wort; and Kava). A succinct summary of the data is provided below, covered under the major psychiatric disorder headings.

4 | MOOD DISORDERS

4.1 | Major depressive disorder

Major depressive disorder (MDD) or "unipolar depression" involves depressed mood or reduced interest or pleasure and is accompanied by at least four other additional symptoms (e.g., weight or appetite change, fatigue, psychomotor agitation, insomnia or hypersomnia, lack of concentration, suicidal ideation, feelings of worthlessness or guilt, and low libido; APA, 2013). According to the World Health Organization (WHO), an estimated 322 million people are currently effected by MDD (including dysthymia), an increase of more than 18% over the 10-year period since 2005, making it the leading cause of ill health and disability worldwide (WHO, 2017). MDD is the psychiatric condition in which the most herbal medicine research has been conducted, with St John's wort representing the vast majority of the research.

TABLE 1 Psychiatric conditions reviewed

Disorder
Mood disorders
Major depressive disorder
Dysthymic disorder
Anxious depression
Seasonal affective disorder
Bipolar disorder
Anxiety disorders
Generalized anxiety disorder
Social phobia
Obsessive–compulsive disorder
Somatoform disorder
Schizophrenia
Attention-deficit hyperactivity disorder

TABLE 2 Herbal medicines reviewed

Herbal medicine	Psychiatric disorders/symptoms studied
Bacopa monniera	GAD
Centella asiatica	Generalized anxiety and stress, GAD
Citrus aurantium	GAD
Crocus sativus	MDD, GAD
Curcuma longa	MDD
Cuscuta spp.	MDD
Hypericum perforatum	MDD, SP, OCD, ADHD, DYS, SOM, SAD, AnxD
Galphimia glauca	GAD
Ginkgo biloba	GAD, SAD, ADHD, BD
Lavandula spp.	MDD
Matricaria recutita	GAD
Melissa officinalis	Generalized anxiety, stress, mood disturbance, SOM
Nepeta spp.	GAD
Panax ginseng	MDD, GAD
Panax quinquefolium	SCHZ, ADHD
Passiflora incarnata	GAD, SOM
Petasites hybridus	SOM
Pinus pinaster	ADHD
Piper methysticum	GAD, SP, AnxD
Rhodiola rosea	MDD, GAD
Scutellaria lateriflora	GAD
Silybum marianum	OCD
Valeriana spp.	GAD, AnxD, SOM
Withania somnifera	SCHZ, BD, GAD

Note. GAD = generalized anxiety disorder; MDD = major depressive disorder; SCHZ = schizophrenia; OCD = obsessive–compulsive disorder; SP = social phobia; DYS = dysthymia; SOM = somatoform disorder; SAD = seasonal affective disorder; BD = bipolar disorder; AnxD = anxious depression.

4.1.1 | *C. sativus* (saffron)

Saffron has been used to improve mood in traditional Persian medicine, with a continual flow of RCTs being conducted in Iran in the past 12 years. Saffron stigma contains an estimated 40 to 50 active therapeutic constituents with high quality saffron containing approximately 30% crocins, 5–15% picrocrocin, and over 5% volatile compounds including safranal (Schmidt, Betti, & Hensel, 2007). In respect to mechanisms of action, preclinical animal models using ethanolic extracts of saffron and its constituents safranal and crocin, have shown antidepressant, anxiolytic, and hypnotic effects (Hosseinzadeh & Noraei, 2009). Crocin's antidepressant activity purportedly acts via reuptake inhibition of dopamine and norepinephrine and safranal's via serotonin reuptake inhibition (Schmidt et al., 2007). Anti-inflammatory and immunological effects have also been revealed in preclinical models (Boskabady & Farkhondeh, 2016; Chiavaroli et al., 2017).

A meta-analysis of published RCTs examining the effects of saffron supplementation on symptoms of depression among participants with MDD was conducted in 2013. The criteria for study selection included adults (aged 18 and older) with symptoms of depression, RCTs (vs. placebo or an antidepressant), assessing the effects on depressive symptoms (Hausenblas, Saha, Dubyak, & Anton, 2013). Five

RCTs were located (two placebo controlled trials and three antidepressant-controlled trials). A significant result with a large effect size was found in favour of saffron treatment versus placebo control in treating depressive symptoms, whereas no significant difference was evidenced between saffron prescription and the antidepressant groups, indicating that both treatments were similarly effective in reducing depression symptoms. The mean Jadad score was 5, indicating that the quality of the studies was high. The authors advised that larger clinical trials of longer duration, particularly by research teams outside of Iran, should be conducted to solidify the benefit of saffron in MDD (Hausenblas et al., 2013).

Since that meta-analysis, another small 12 week double-blind RCT (*n* = 60) revealed a significant effect for 50 mg of saffron per day in improving mood and reducing anxiety over placebo (Mazidi et al., 2016). A 6 week double-blind RCT (*n* = 40) also showed that saffron (30 mg per day) was equivalent to the antidepressant fluoxetine in postpercutaneous coronary intervention patients with depression (Shahmansouri et al., 2014); whereas another small (*n* = 40) 4 week double-blind RCT assessing saffron augmentation (30 mg per day) with fluoxetine showed no effect over placebo (Sahraian, Jelodar, Javid, Mowla, & Ahmadzadeh, 2016).

Although the weight of this evidence is encouraging, the short study time (4 to 6 weeks), small sample size (30–60 patients), and deficit of Western study sites limit complete confidence in the results. One caveat in adopting saffron into the phytotherapeutic materia medica is that the cost of saffron may be prohibitive, although there is the potential to also use a blend which includes the stigma and the cheaper aerial parts.

4.1.2 | *Curcuma longa* (turmeric)

In addition to being employed as a common cooking spice, turmeric has been used in traditional Ayurvedic and Chinese medicine for centuries to treat a range of health conditions (Kunnumakkara et al., 2017). The main active constituent is regarded as being curcumin (Al-Karawi, Al Mamoori, & Tayyar, 2016; Lopresti, 2017), which possesses anti-inflammatory, antioxidant, neuroprotective, and monoaminergic modulatory activities (He et al., 2015; Kunnumakkara et al., 2017). As inflammation is being increasingly regarded as being involved as a causative factor in a subset of people suffering from depression (Berk et al., 2013), turmeric has a potential use as a strong anti-inflammatory (although absorption and bioavailability can be an issue).

A meta-analysis in 2017 by Ng, Koh, Chan, and Ho (2017) included six clinical trials (4 to 8 weeks in duration) involving 377 patients with depression, comparing either turmeric or curcumin to placebo. Results revealed a significant effect in favour of turmeric in reducing depressive symptoms. Significant anti-anxiety effects were also reported in three of the clinical trials. Two turmeric studies are worth further discussion. One 6 week RCT (Yu, Pei, Zhang, Wen, & Yang, 2015) involving 108 male adults in China, tested 1,000 mg of curcumin per day versus placebo as an augmentation to escitalopram. Results showed a significant reduction of depression on the Hamilton Depression Rating Scale (HAM-D) and the Montgomery–Asberg Depression Rating Scale (MADRS) in favour of turmeric

outperforming placebo. Interestingly, the curcumin decreased inflammatory cytokines (interleukin-1β and tumour necrosis factor-α) and salivary cortisol concentrations, while increasing plasma brain-derived neurotrophic factor levels, compared with placebo. The other study concerns a four-arm double-blind RCT design to evaluate low-dose curcumin extract (250 mg twice per day), a high-dose curcumin extract (500 mg twice per day), a combined low-dose curcumin plus saffron extract (15 mg twice per day), or placebo, for 12 weeks in 123 participants with MDD (Lopresti & Drummond, 2017). Results revealed that active treatment outperformed placebo in reducing both depression and anxiety scores, with no difference found between the differing doses of curcumin or the curcumin/saffron combination.

4.1.3 | *H. perforatum* (St John's wort)

The flowering tops of St John's wort (SJW) has been used traditionally for a variety of nervous system disorders and has been used over the past decades in certain European countries as a first-line treatment of MDD. The mechanism of SJW's antidepressant action is regarded to involve nonselective inhibition of the neuronal reuptake of serotonin, dopamine, norepinephrine, Gamma-aminobutyric acid (GABA), and L-glutamate, decreased degradation of neurochemicals and a sensitization of and increased binding to various receptors (e.g., GABA, glutamate, and adenosine; Butterweck, 2003; Mennini & Gobbi, 2004; Zanoli, 2004). Human studies have also found that SJW modulates salivary and serum cortisol levels, also having a slight effect on growth hormone levels (Franklin, Hafizi, Reed, Hockney, & Murck, 2006; Schüle, Baghai, Ferrera, & Laakmann, 2001). Hyperforin, hypericin, and various flavonoids appear to be responsible for the neurochemical modulation (Butterweck, 2003; Laakmann, Schüle, Baghai, & Kieser, 1998; Zanoli, 2004). As occurs in all herbal medicines, synergy between constituents may be a vital aspect of efficacy (Williamson, 2001), as evidence demonstrates that the absence of rutin, a simple flavonoid constituent in SJW, reduces the antidepressant activity (Wurglics & Schubert-Zsilavecz, 2006). Regardless, there is still controversy, however, regarding the optimum phytochemical standardization required to exert maximal antidepressant activity, and there are issues with extrapolating preclinical data to humans (as certain SJW constituents do not cross the blood–brain barrier or display in vitro effects at very high human-equivalent doses; Cott, 2010).

A 2008 Cochrane Review meta-analysis of SJW RCTs (Linde, Berner, & Kriston, 2008) revealed a significant rate of response to treatment from 18 combined studies in favour of SJW versus placebo and an equivalent effect to selective serotonin reuptake inhibitors (SSRIs). Another meta-analysis conducted around the same time by Rahimi, Nikfar, and Abdollahi (2009) also revealed a significant response in favour of SJW over placebo, with a small weighted mean difference between treatments. The comparison with SSRIs showed a nonsignificant difference between treatments for mean reduction of HAM-D score from baseline.

Due to publicized trial results (cf. Hypericum Depression Trial Study, 2002; Sarris, Fava, Schweitzer, & Mischoulon, 2012) indicating that SJW was no more effective than placebo (although slightly

more effective than sertraline), the herbal medicine is commonly now only recommended for mild to moderate depression, due to clinical concerns of using it in more severe MDD (Clement, Covertson, Johnson, & Dearing, 2006; Lawvere & Mahoney, 2005; Linde, Mulrow, Berner, & Egger, 2005; Shelton et al., 2001). The concerns however may not be entirely well-placed in respect to SJW for treating moderate to severe depression (HAM-D > 20); as it can be noted that a 6 week 2005 RCT (n = 251) comparing SJW extract WS 5570 (900 mg/day) to paroxetine (20 mg/day) and placebo in moderate to severe depression (HAM-D ≥ 22) demonstrated SJW's therapeutic superiority with a 3-point differential reduction on the HAM-D (Szegedi, Kohnen, Dienel, & Kieser, 2005). A similar result was found in terms of 900 mg/day of LI-160 SJW extract being superior to fluoxetine in a three-arm double-blind RCT (n = 135); although it only trended towards significant benefit over placebo (Fava et al., 2005).

There is also little evidence on the efficacy and safety of SJW in treating adolescents with MDD. Two small open-label trials of SJW were identified where it was trialled in adolescents less than 17 years old (Findling et al., 2003; Simeon, Nixon, Milin, Jovanovic, & Walker, 2005). Although the results of these trials were promising, neither had a placebo group nor randomization, and there was a high percentage of dropouts due to continuing depression or noncompliance. No definitive affirmation of efficacy can be reached from these data.

The safety profile of SJW is very sound, with a systematic review detailing that the degree of adverse effects in 35,562 pooled patients was 0–5.7%, which was comparable with placebo (Knuppel & Linde, 2004). In a 2006 review of 16 postmarketing surveillance studies (n = 34,834: Schulz, 2006), SJW was deemed to be 10-fold safer than synthetic antidepressants (adverse effects 0.1% to 2.4%). Apart from rare idiosyncratic reactions, most adverse effects involve reversible dermatological and gastrointestinal effects. Serotonin syndrome has been documented in case studies (Knuppel & Linde, 2004; Rodriguez-Landa & Contreras, 2003); however, a direct pharmacodynamic interaction has not yet been established. Case studies have detailed possible SJW-induced mania and psychosis (covered later). Overall, as detailed above, SJW has demonstrated equal efficacy to pharmaceutical antidepressants; however, it presents with a more favourable side effect profile.

The main caveat to prescribing SJW is over concerns with potential drug interactions, including a tendency to reduce the serum levels of many pharmaceuticals. Current evidence suggests that this is due to hyperforin increasing the expression of the pregnane X receptor, which increases P-glycoprotein expression (the drug efflux pump; Dresser, Schwarz, Wilkinson, & Kim, 2003; Izzo, 2004; Moore et al., 2000). It should be noted that low-dose hyperforin preparations (<4 mg of hyperforin) may not affect P-glycoprotein expression and hence may be safer (Izzo, 2004; Mueller et al., 2006).

4.1.4 | *Nepeta menthoides* (catmint) and *Cuscuta spp.* (dodder)

Catmint and dodder are used in Persian medicine for a range of ailments. Currently, there is no clear scientific evidence underpinning

any antidepressant activity; however, a 4 week Iranian study assessed a freeze-dried aqueous extract of catmint (800 mg per day) compared with sertraline (100 mg per day) in the treatment of 72 patients with Diagnostic and Statistical Manual for Psychiatric Disorders Edition 5 (DSM-5) diagnosed MDD (Kolouri et al., 2016). The results revealed a superior effect in the reduction of Beck Depression Inventory (BDI)-II scores in catmint group compared with sertraline, as well as a lower short-term recurrence rate (2 weeks post-intervention). The adverse events (drowsiness, insomnia, decreased libido, and constipation) were also less frequent in the catmint group relative to sertraline. Another clinical trial using catmint (800 mg per day) in combination with dodder (2,000 mg per day) has been conducted in 43 participants with MDD (Firoozabadi, Zarshenas, Salehi, Jahanbin, & Mohagheghzadeh, 2015). The 8 week randomized triple-blind controlled clinical trial conducted in Iran, randomly assigned the patients into three groups: Group A (catmint capsules and conventional drugs), Group B (treated with dodder capsules and conventional drugs), and Group C (treated only with conventional drugs). Results on the BDI-II and the HAM-D showed a superiority of the adjunctive catmint and dodder groups compared with medication as usual.

4.1.5 | *Panax ginseng* (Korean ginseng)

The root of Korean ginseng has been used for millennia across Asia for its perceived "tonic" and adaptogenic properties, being used particularly in the elderly. Korean ginseng and its active constituents, the ginsenosides, have shown potential antidepressant effects in a variety of animal studies and in patients with stress-related somatic symptoms, although the exact mechanisms are currently unknown (Kim, Kim, Jeong, & Kim, 2011). One 8 week prospective open label study, which involved 35 female outpatients who were in remission from a major depressive episode but still experiencing residual symptoms, utilized Korean Red Ginseng at doses of 3 g/day (Jeong et al., 2015). Results revealed that the women reported significant decreases in depressive symptoms on the Depression Residual Symptom Scale and MADRS over the 8 week period. Somatic symptoms measured on the Depression and Somatic Symptom Scale were also attenuated significantly during the study period.

4.1.6 | *Lavandula spp.* (lavender)

Lavender has a long traditional use in treating nervous system disorders, in principle due to its bioactive volatile oils (Felter & Lloyd, 2006 [1898]). The psychopharmacology underpinning any potential antidepressant activity is currently unknown; however, its anxiolytic effects are well-known, and this in part is due to the volatile component linalool (Woelk & Schlafke, 2010). An initial small study assessed lavender's antidepressant activity. The 4 week RCT was conducted comparing lavender tincture (1:5 50% alcohol, 60 drops) against imipramine, in 45 patients with a HAM-D rating of at least 18 (Akhondzadeh et al., 2003). The results demonstrated that although the herbal extract was less effective than its synthetic counterpart, the combination of both was more effective than imipramine alone, indicating a synergistic effect. A clinical trial involving 80 MDD patients in Iran prescribed 20 mg of citalopram twice a day for 8 weeks,

with one group being additionally given two cups of dried lavender infusion (5 g) compared with no additional treatment (Nikfarjam, Parvin, Assarzadegan, & Asghari, 2013). After 8 weeks, there was a small but significant difference in favour of the lavender add-on group. The lavender tea was well tolerated, with no difference in side effects between the groups. A more recent 6 week three-arm double-blind RCT involving 120 patients tested lavender augmentation (1,500 mg infusion twice daily) with venlafaxine (37.5 mg) versus venlafaxine with placebo (peppermint infusion twice daily) and control (venlafaxine only; Nikfarjam, Rakhshan, & Ghaderi, 2017). Results revealed that there was no significant difference between adding "placebo" or lavender to venlafaxine, with both being effective in reducing depression compared with standard treatment (although it should be noted that the "placebo" peppermint also has medicinal properties). High quality supportive research has also been conducted on an oral standardized lavender oil (Silexan); however, this review only focuses on whole Galenical plant extracts.

4.1.7 | *Rhodiola rosea* (roseroot)

One of the most promising herbal medicines in the treatment of depression is roseroot, a stimulating adaptogen capable of exerting antidepressant activity (Kelly, 2001; Kucinskaite, Briedis, & Savickas, 2004). High-pressure liquid chromatography has identified the cinnamyl alcohol betavicianidines, rosavin, rosin, and rosarin as being specific to roseroot (Bykov, Zapesochnaya, & Kurkin, 1999; Dubichev, Kurkin, Zapesochnaya, & Vorontsov, 1991; Kurkin & Zapesochnaya, 1986). Antidepressant activity of roseroot has been purported to occur via mono-amine oxidase A modulation (Van Diermen et al., 2009) and via modulation of cortisol (Darbinyan et al., 2007; Olsson, Von Scheele, & Panossian, 2009). A clinical study investigating the influence of roseroot (370 and 555 mg doses) on various mental and biological parameters of 161 19–21 year olds, discovered a pronounced antifatigue effect (Shevtsov et al., 2003). This adaptogenic activity in combination with purported monoamine modulation indicates a novel application in monopolar depression (Stancheva & Mosharrof, 1987, cited by Kelly, 2001).

An initial open label study of 128 depressed patients given 150 mg 3 times per day of roseroot or placebo, showed that two thirds of those taking roseroot had a significantly improved mood (Brichenko & Skorokhova, 1987; Saratikov & Krasnov, 1987). A double-blind RCT of a standardized extract of roseroot (SHR-5®) as a monotherapy for 89 adults who met DSM 4th Edition, Revised (DSM-IV-TR 2000) criteria for mild to moderate depression, found that those given 340 or 680 mg/day of the extract for 6 weeks showed significantly greater improvements in mean HAM-D scores compared with the placebo group (Darbinyan et al., 2007). A more recent study of a standardized roseroot extract in MDD sought to determine whether it was more effective than sertraline and placebo, in a 12 week double-blind RCT (Mao et al., 2015). Fifty-seven participants were recruited, with results revealing a nonsignificant difference between treatments for depression and anxiety outcomes. The reduction of depression and anxiety did however favour the antidepressant, although the side effects were far less pronounced in the roseroot group compared with the sertraline.

4.2 | Dysthymic disorder

Dysthymic disorder (DD) is characterized in the DSM-5 as a persistent low mood (although not meeting the criteria of MDD) occurring for at least 2 years on more days than not (APA, 2013). Only one study was located assessing the herbal treatment of dysthymia. A 2006 double-blind RCT (n = 150) using a standardized SJW extract PM235 (810 mg/day) observed that although significant improvement occurred in nondysthymic depressed patients, no statistical improvement was discovered in ICD-10 depressed dysthymic patients as assessed via the HAM-D, a visual analogue scale (VAS) and the BDI (Randløv et al., 2006). As discussed in Randløv et al. (2006), it is possible that herbal interventions may not succeed in ameliorating persistent dysthymic mood, as this may be a reflection of an established melancholic personality trait in certain people.

4.3 | Seasonal affective disorder

Controversy exists regarding the exact diagnostic classification of seasonally provoked mood disorders (Magnusson & Partonen, 2005), with seasonal affective disorder (SAD) being the term commonly adopted (APA, 2013). To date, three trials have been performed using herbal agents in SAD. Two open-label trials using SJW alone (300 mg thrice daily) and SJW plus light therapy found there was a significant reduction of winter-provoked depression, although there was no statistical difference between the two treatments (Martinez, Kasper, Ruhrmann, & Moller, 1994; Wheatley, 1999). A more rigorous small-sample doubled-blind RCT using a twice daily dose of the ginkgo extract PN 246 (containing 24 mg flavone glycosides and 6 mg terpene lactones) to prevent the onset of SAD in 27 people, found no difference between the active and placebo group on the MADRS and VAS outcomes (Lingærde, Føreland, & Magnusson, 1999). Currently, there is no supportive evidence available for any specific herbal intervention to confidently treat SAD, and light therapy is the often regarded as a first-line intervention (Gordijn, Mannetje, & Meesters, 2012).

4.4 | Depression with anxious symptoms

Although no diagnosis of depression with anxious symptoms (AnxD) is identified in the DSM-5, anxiety symptoms are endemic in depression, and the ICD-10 regards this as "mixed anxiety and depression" (Kessler et al., 2003; Sheehan et al., 1998). Further, true comorbidity of depressive and anxious conditions commonly occurs (Hunt, Slade, & Andrews, 2004; Sartorius, Ustun, Lecrubier, & Wittchen, 1996). In cases where there is a combination of depression and anxiety, adjunctive anxiolytic medications with antidepressants have been suggested as a strategy to address acute anxiety, as the thymoleptic effect of antidepressant medications often takes 2 to 3 weeks to occur (Baghai, Volz, & Möller, 2006; Nemeroff, 2003). Two studies were located: an open, practice-orientated study using SJW alongside low- or high-dose *Valeriana officinalis* (Valerian) extract to treat AnxD demonstrated success, with results tending to suggest more effectiveness in the higher dose Valerian group (although this was not confirmed statistically; Müller, Pfeil, & Von Den Driesch, 2003). A 2009 double-blind cross-over RCT involving 28 adults with MDD and co-occurring anxiety was given a combination of SJW

(1.8 mg 3× a day; 2,970 mg of hypericin) and Kava (2.66 mg 3× a day; 150 mg of kavalactones) after a placebo run-in of 2 weeks (Sarris, Kavanagh, Deed, & Bone, 2009). Results assessing the effects of the herbal combination in the two controlled phases, each of 4 weeks, found no significant Group × Time interaction for any depression or anxiety outcome.

5 | ANXIETY DISORDERS

5.1 | Generalized anxiety disorder and nonspecified anxiety

Generalized anxiety disorder (GAD) is diagnosed in persons with excessive worry and anxiety, accompanied by more than three somatic symptoms (e.g., tension and irritability) that occurs more days than not, for a period of at least 6 months (APA, 2013). Anxiety represents the broadest area of research of herbal medicines in psychiatric disorders, with the most individual phytomedicines possessing documented anxiolytic activity (Sarris et al., 2013a, 2013b). Kava is the herbal medicine that has been the most extensively researched anxiolytic, albeit with previous concerns existing regarding its safety due to cases of hepatotoxicity.

5.1.1 | *Bacopa monniera* (Brahmi)

Although Brahmi is usually studied for its reputed cognitive enhancing activity, the plant has traditional use in treating anxiety and insomnia and even has been recommended in years past for the antiquated diagnosis of "insanity." Preclinical research has demonstrated various CNS actions including nootropic, antidepressant, anxiolytic, and antioxidant effects. Neurologically focused preclinical studies have shown that Brahmi modulates acetylcholine, dopamine, serotonin, and noradrenalin pathways (Charles, Ambigapathy, Geraldine, Akbarsha, & Rajan, 2010) and increases protein kinase activity within the hippocampus (Singh & Dhawan, 1997). The key chemical constituent is regarded as bacoside A. One study was located assessing Brahmi effect on anxiety, the 2001 double-blind RCT using 300 mg of Brahmi demonstrating a marked reduction of state anxiety compared with placebo after 12 weeks of treatment (Stough et al., 2001).

5.1.2 | *Centella asiatica* (gotu kola)

Gotu kola has been used for centuries in Ayurvedic and traditional Pan-Pacific medicine for a variety of therapeutic applications, including treatment of anxious and depressive complaints. Gotu kola (and the key constituents) has displayed GABAergic effects revealed in studies analysing GABA-transaminase (GABA-T) and glutamic acid decarboxylase activity (Awad et al., 2007). A double-blind, placebo-controlled study was undertaken to evaluate the anxiolytic activity of gotu kola via the acoustic startle response in 40 healthy participants (Bradwejn, Zhou, Koszycki, & Shlik, 2000). Participants were randomly assigned to receive either a large single 12 g orally administered dose of gotu kola or placebo. Compared with placebo, gotu kola significantly attenuated the peak acoustic startle response amplitude 30 and 60 min after treatment, thereby indicating anxiolytic activity. Currently, no robust RCTs exist; however, an open label study of 500 mg of gotu kola twice

daily for 2 months in 33 patients with GAD (Jana, Sur, Maity, Debnath, & Bhattacharyya, 2010) revealed significant improvements in anxiety following 60 days of treatment on the Hamilton Anxiety Rating Scale (HAM-A), along with significant reductions in secondary measures of stress and depression.

5.1.3 | *Galphimia glauca* (galphimia)

In traditional Mexican and Central American cultures, the leaves and stem from galphimia are used for nervous disorders, with the serotonergic galphimine B being regarded as an active constituent (Jimenez-Ferrer, Herrera-Ruiz, Ramirez-Garcia, Herrera-Arellano, & Tortoriello, 2011). It has been shown to interact with serotonergic transmission via the dorsal hippocampus in rats, by increasing the frequency of neuronal discharge in CA1 cells, activating the 5HT(1A) receptors (Jimenez-Ferrer et al., 2011). In a 4 week double-blind RCT, an aqueous extract of galphimia was administered to 153 patients with a DSM-IV diagnosis of GAD (Herrera-Arellano et al., 2007). The positive control group received 1 mg of lorazepam in capsule form twice daily versus the galphimia group receiving 310 mg of the extract twice daily. Results revealed no significant difference between groups in the anxiolytic effect found across time. No significant side effects were noted in the galphimia group, whereas 21% of people in the lorazepam group experienced excessive sedation. In a follow-up study (Herrera-Arellano et al., 2012), 191 patients with a DSM-IV diagnosis of GAD were administered 3.48 g of dried galphimia per capsule (0.35 or 0.7 mg/day of galphimine B), versus 1 mg to 2 mg of lorazepam over a 15 week period. A significantly greater reduction in HAM-A score occurred for galphimia treatment in comparison with lorazepam over the course of the clinical trial.

5.1.4 | *Matricaria recutita* (chamomile)

The flowering tops of chamomile is widely consumed throughout the Western world in tea form, with a history of traditional use as a mild relaxant. Preclinical research has revealed a range of effects considered to be mediated via modulation of the GABA system (Avallone et al., 2000; Awad et al., 2007). One of the active constituents is the flavone apigenin, which is a benzodiazepine receptor ligand with anxiolytic activity (Salgueiro et al., 1997; Viola et al., 1995). An 8 week double-blind RCT involving 57 GAD patients showed significantly greater reductions in anxiety from chamomile (220 mg, 1 to 4 times daily) on the HAM-A scale when compared with the placebo group (Amsterdam et al., 2009). A post hoc analysis of the same sample found that chamomile may also reduce comorbid depression (HAM-D rated) in anxious patients (Amsterdam et al., 2012).

Two further clinical trials reported both short- and long-term (i.e., 8 and 38 weeks, respectively) effects of anxiety treatment using 1,500 mg of chamomile (500 mg capsule 3 times daily) in 179 patients with GAD. At Week 8, 58% of patients met the criteria for clinical response in the chamomile group, with significant reductions in mean anxiety (GAD-7) across the entire sample (Keefe, Mao, Soeller, Li, & Amsterdam, 2016). For the long-term study, clinical responders were randomly assigned to continued active or placebo treatment for a further 26 weeks. GAD relapse rates were 25.5% in the placebo group, and only 15.2% in the continued treatment group (Mao et al., 2016).

Although neither the difference in relapse rates nor the HAM-A or the Beck Anxiety Inventory symptom reductions, reached statistical significance.

5.1.5 | *Melissa officinalis* (lemon balm)

Lemon balm has traditional usage as a mild sedative and spasmolytic agent. In vitro studies have revealed anxiolytic activity via elevation of GABA levels from inhibition of GABA-transaminase (Awad et al., 2007; Awad, Muhammad, Durst, Trudeau, & Arnason, 2009). A double-blind RCT was conducted with 20 participants who were given single doses of 300, 600, and 900 mg of lemon balm or a matching placebo at 7-day intervals. Self-rated calmness, as assessed by Bond–Lader mood scales was elevated at the earliest time points by the lowest dose, whereas perceived alertness was significantly reduced at all time points following the highest dose (Kennedy, Scholey, Tildesley, Perry, & Wesnes, 2002). A double-blind cross-over RCT (*n* = 18) using two separate single doses of lemon balm extract (300 and 600 mg) and placebo (Kennedy, Little, & Scholey, 2004), determined that acute dosing of lemon balm demonstrated a significant increase in self-rated calmness and reduced alertness in subjects via a defined intensity stressor simulation test. A later study of a similar design tested a lemon balm and valerian extract combination (600, 1,200, or 1,800 mg pills consisting of three parts valerian extract to two parts lemon balm) against placebo in 24 healthy volunteers at three time points (1, 3, and 6 hr post-test; Kennedy, Little, Haskell, & Scholey, 2006). The results demonstrated that although none of the Bond–Lader scores were significantly different between groups, the lowest dose of the combination ameliorated the anxiogenic effects of the defined intensity stressor simulation after 3 and 6 hr, whereas the higher doses failed to outperform placebo (with the 1,800 mg dose in fact causing increased "state" anxiety after 1 hr).

A combined lemon balm leaf (320 mg per day) and valerian root (640 mg) preparation was investigated in a large sample 4 week open, multicentre study in children less than 12 years (*n* = 918) suffering from restlessness and nervous dyskoimesis (Muller & Klement, 2006). The primary symptoms of dyssomnia and restlessness were reduced from "moderate/severe" to "mild" or "absent" in most of the children, with 70.4% of the patients with restlessness improving. Both parents and investigators assessed efficacy as "very good" or "good" (67.7% and 60.5%, respectively).

5.1.6 | *Passiflora incarnata* (passionflower)

Passionflower has been used in traditional medicine in the Americas "to allay restlessness and overcome wakefulness, when these are the result of exhaustion or the nervous excitement of debility" (Felter & Lloyd, 2006 [1898]). The principle constituents include alkaloids such as chrysin, flavonoids, and phenolic compounds (Wohlmuth, Penman, Pearson, & Lehmann, 2010). GABAergic modulation has been posited as occurring via GABA reuptake inhibition, and modulation of the GABA-a receptor complex (Appel et al., 2011; Nassiri-Asl, Zamansoltani, & Shariati-Rad, 2008). An initial Iranian RCT using passionflower extract in a sample of participants with GAD (*n* = 36) showed that the plant was as effective (with less side effects) as oxazepam (30 mg/day) in reducing anxiety (Akhondzadeh et al., 2001).

Since then, six studies involving human populations were found; four examined effects on pre-operative anxiety via RCT designs (Aslanargun, Cuvas, Dikmen, Aslan, & Yuksel, 2012; Dantas, De Oliveira-Ribeiro, De Almeida-Souza, & Groppo, 2017; Kaviani, Tavakoli, Tabanmehr, & Havaei, 2013; Movafegh, Alizadeh, Hajimohamadi, Esfehani, & Nejatfar, 2008), all reporting significant benefits from passionflower in comparison with placebo and non-inferiority to pharmaceutical comparators.

Most recently, this effect was observed in a double-blind RCT of 40 dental surgery patients (Dantas et al., 2017), showing passionflower (260 mg) orally administered 30 min before dental surgery reduced subjective anxiety along with physiological indicators (i.e., blood pressure and heart rate). This occurred to the same extent as midazolam, however, with fewer cognitively impairing side effects. It is worth noting also that *Citrus aurantium* (orange blossom) in 60 patients undergoing minor operation also was found in a double-blind RCT to significantly reduce pre-operative anxiety compared with a saline placebo (Akhlaghi et al., 2011).

5.1.7 | *P. methysticum* (kava)

The South Pacific medicinal plant kava has traditional uses as a relaxant (and an inebriant at higher doses) and is used in modern phytotherapy as a treatment for anxiety. Kava's mechanisms of action are considered to involve interaction of the active constituents, the kavalactones, with GABA voltage-gated sodium ion channels, enhanced ligand binding across GABA-a receptor subtypes, and reduced excitatory neurotransmitter release via blockade of calcium ion channels (He, Lin, & Lian, 1997; Magura, Kopanitsa, Gleitz, & Al, 1997; Mathews, Etheridge, Valentine, & Al, 2005).

A 2003 Cochrane Review of double-blind RCTs using kava mono-preparations (60–280 mg of kavalactones) in a variety of anxiety conditions, included 12 trials that met the inclusion criteria (Pittler & Ernst, 2003). Results of the review documented a statistically significant anxiolytic activity compared with placebo in all but one trial, demonstrating that kava is an effective short-term treatment of anxiety. Meta-analysis of seven homogenous trials using HAM-A as the primary outcome found that kava reduced anxiety significantly over placebo. Subsequent short-term double-blind RCTs using water-soluble rootstock noble kava cultivar extracts (between 120 and 240 mg of kavalactones per day) have also further confirmed these findings (Sarris et al., 2009; Sarris, Stough, et al., 2013) in chronic generalized anxiety and GAD.

An insufficiency of trials exists studying the efficacy of kava compared with synthetic agents such as benzodiazepines or antidepressants. One study assessed kava in comparison with buspirone or opipramol in treating GAD using an 8 week (*n* = 129) double-blind RCT design (Boerner et al., 2003). The results of the study found no significant difference between kava and buspirone or opipramol regarding all efficacy and safety measures. Seventy five percent of patients were classified as responders (50% reduction of HAM-A score) in each treatment group, with 60% achieving full remission.

Concerns of hepatotoxicity have emerged in recent years prompting postmarketing, clinical, and toxicology studies to be performed to assess the safety of the plant. A 2002 review of kava was conducted to assess the plant's safety profile via literature searches of four electronic databases, papers' reference lists, spontaneous reporting schemes of the WHO and national drug safety bodies, and 10 manufacturers of medicinal preparations (Stevinson, Huntley, & Ernst, 2002). The data suggest that adverse events are in general very rare, mild, and usually reversible. Since this review over the past 15 years, there have been no obvious further human liver toxicity associations come to light in the literature. Previous liver issues found with German kava products that may be due in part to the use of aerial parts and root and stem peelings, and poorly prepared raw material (Teschke, Sarris, Glass, & Schulze, 2011). The WHO commissioned a report assessing the risk of kava products (Coulter, Tamayo, Sotheeswaran, Ulbricht, & World Health Organization, 2007). Recommendation 2.1.3 from this report suggested that products from water-based suspensions be developed and tested in clinical trials and that these preparations be used preferentially over acetonic and ethanolic extracts. Thus, the use of standardized formulations using peeled rootstock extracts of a noble cultivar (such cultivars are higher in kawain and dihydrokavain and lower in dihydromethysticin) is recommended. For further discussion on this, see Teschke, Sarris, Glass, et al. (2011) and Teschke, Sarris, and Lebot (2011).

5.1.8 | *Scutellaria lateriflora* (scullcap)

Scullcap is a plant medicine that has traditional use as a sedative in various nervous system disorders in Native American and Eclectic medicine. Preclinical models have identified the compounds baicalin and baicalein purported to be involved its anxiolytic activity via binding to the benzodiazepine site of GABA(A) (Awad et al., 2003). Two human studies using scullcap extract were found, both in nonclinical samples. In a double-blind crossover RCT (*n* = 43) in which participants were initially randomized into either 2 weeks of 350 mg of scullcap extract (3 times per day) or a placebo comparator, Brock, Whitehouse, Tewfik, and Towell (2014) reported no difference in anxiety outcomes between groups. This was ascribed to both a "floor effect," as these healthy volunteers were mostly non-anxious at baseline, as well as baseline heterogeneity between groups. An older poorly reported double-blind cross-over RCT of healthy adults (*n* = 19) suggested scullcap may reduce symptoms of anxiety and tension after acute administration compared with control, although this was determined without significance testing (Wolfson & Hoffmann, 2003).

5.1.9 | *Ginkgo biloba* (ginkgo)

Although ginkgo is used therapeutically to treat cognitive decline, peripheral arterial disease, and tinnitus, studies have noted that mood modulation can occur in cognitively impaired subjects (Fehske, Leuner, & Muller, 2009). The anxiolytic effects of ginkgo extract and its four terpenoid components (ginkgolide-A, ginkgolide-B, ginkgolide-C, and bilobalide) were have an anxiolytic effect in animal models (Kuribara, Weintraub, Yoshihama, & Maruyama, 2003). A 2006 double-blind RCT (*n* = 107) was conducted using EGb 761 extract (480 or 240 mg per day) or placebo for 4 weeks in adults with GAD or adjustment disorder with anxious mood, as assessed via DSM-III-R (Woelk, Arnoldt, Kieser, & Hoerr, 2007). Results showed that the participants' HAM-A total scores decreased significantly in both the 480 mg per

day and 240 mg per day ginkgo groups, relative to placebo, in a dose-dependent manner.

5.1.10 | *Rhodiola rosea* (roseroot)

Although roseroot is commonly studied for its antifatigue and mood-elevating effects (as detailed above), two studies are available for review in the area of anxiety. A 2 week clinical trial involved 80 mildly anxious patients who were given either 2 × 200 mg per day of roseroot (Vitano) or a nonplacebo control condition (no treatment) (Cropley, Banks, & Boyle, 2015). Results showed that relative to the control, the roseroot group demonstrated a significant reduction in self-reported, anxiety, stress, anger, confusion, and depression and improvements in total mood. Caution needs to be extended to this finding due to the lack of a credible control. Roseroot (SHR-5) has also been studied in a small pilot 10 week open-label design (*n* = 10) in participants with a GAD (Bystritsky, Kerwin, & Feusner, 2008). Results revealed that mean HAM-A scores were significantly different at the end of treatment compared with baseline, with five out of 10 participants regarded as responders to treatment. As this study was uncontrolled, conclusions as to its efficacy need to be tempered.

5.1.11 | *Withania somnifera* (ashwagandha)

Classified in Ayurvedic medicine as a "rasayana," a medicine used to enhance physical and mental performance and ward off disease, ashwagandha has been adopted into Western herbal material medica for its use in nervous system and endocrine disorders. An animal study has observed adaptogenic effects of ashwagandha via a stress-inducing procedure, revealing attenuation of stress-related parameters (cortisol levels, mental depression, and sexual dysfunction; Bhattacharya & Muruganandam, 2003). The purported active constituents are considered to be the withanolides, which have been shown to possess GABA-mimetic properties (Andrade, 2009; Bhattacharya, Bhattacharya, Sairam, & Ghosal, 2000).

In human studies, a recent systematic review by Pratte, Nanavati, Young, and Morley (2014) discussed previous studies of ashwagandha on anxiety/stress outcomes. They identified five human RCTs with 400 participants. All five trials reported at least one significant benefit of the herbal medicine in comparison with control conditions for anxiety- and/or stress-related outcomes. The doses of the herbal medicine ranged from 125 to 1,200 mg per day, with trials being between 6 to 16 weeks. Since this review, one further eligible study has been conducted; a double-blind RCT in 52 people with chronic stress, comparing 600 mg of ashwagandha extract per day to placebo over 8 weeks (Choudhary, Bhattacharyya, & Joshi, 2017). Results revealed significantly greater reductions in stress outcomes from the plant medicine, corresponding with significant decreases in salivary cortisol (a stress/anxiety biomarker).

5.2 | Social phobia

Social anxiety disorder (social phobia) is characterized by persistent fear of social or performance situations in which marked stress and or embarrassment occurs (APA, 2013). There is avoidance of these situations and significant interference with the social functioning. Herbal medicine in the treatment of social phobia has been documented

(Boerner, 2001). A case study of a 37-year-old female patient suffering from GAD, and both simple and social phobias achieved nearly complete remission after 6 months of treatment with three tablets of LI 150 Kava extract (equivalent to 135 mg of kavalactones per day). In this updated review, only one clinical study trialling a plant medicine in social phobia was still found. A double-blind RCT using SJW (flexible-dose 600–1,800 mg daily) in 20 people with social phobia (as assessed via the Liebowitz Social Anxiety Scale), revealed no significant differential impact over placebo, although a trend towards improvement was demonstrated (K. a. P. Kobak, Taylor, Warner, & Futterer, 2005).

5.3 | Obsessive–compulsive disorder

The primary features of obsessive–compulsive disorder (OCD) are unreasonable recurrent obsessions or compulsions that are sufficiently severe to consume time and cause marked distress (APA, 2013). A small sample 12 week open-label exploratory study was conducted evaluating SJW (450 mg 0.3% hypericin 2/day) in the treatment of OCD patients (*n* = 12; Taylor & Kobak, 2000). The results demonstrated a significant change of 7.4 points on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) after 12 weeks, with five patients (42%) being rated "much" or "very much improved," six (50%) were "minimally improved," and one (8%) had "no change" on the clinician-rated Clinical Global Impressions (CGI)-scale. A later study sought to validate these results in a 12 week double-blind RCT (K. a. A. Kobak, Taylor, Bystritsky, et al., 2005). SJW (LI 160) at a flexible dose of 600–1,800 mg/day or placebo was administered to 60 adults with OCD. SJW did not ameliorate OCD on the Y-BOCS (3.43) in comparison with placebo (3.60), or differentially affect clinician rating.

A double-blind RCT using *Silybum marianum* (milk thistle), a traditional Mediterranean and Persian plant, was conducted by Iranian researchers to assess its effects on OCD (Sayyah, Boostani, Pakseresht, & Malayeri, 2010). The putative anti-OCD effects of milk thistle may be attributable to the flavanoid complex silymarin (silibinin a key constituent), which in preclinical studies has been found to increase serotonin levels in the cortex (Osuchowski, Johnson, He, & Sharma, 2004), and ameliorate decreases in dopamine and serotonin in the prefrontal cortex and hippocampus associated with methamphetamine abuse (Lu et al., 2010). The study involved 35 participants with a Y-BOCS score of >21 who were randomly assigned 200 mg of milk thistle leaf extract (standardization and chemical profile not detailed by researchers) or 10 mg of fluoxetine 3 times daily for 8 weeks (Sayyah, Boostani, Pakseresht, & Malayeri, 2010). Results revealed no significant difference between treatments from baseline to Week 8. An 8 week double-blind RCT using a valerian extract (765 mg per day) among 31 adults with OCD (DSM-IV diagnosed) also found that the plant medicine significantly reduced symptoms of the disorder (Pakseresht, Boostani, & Sayyah, 2011).

5.4 | Somatoform disorders

The essential feature of somatoform disorders is the presence of physical (somatic) symptoms that cause clinically significant distress or social/occupational impediment that are not explained by a general

medical condition or substance (APA, 2013). The diagnosis of somatoform disorders is problematic, as it is difficult to distinguish between a subjective rating that is not open to direct observation, and it is difficult to distinguish between a psychosomatic and a purely physical presentation (Bradfield, 2006; Kroenke & Rosmalen, 2006; Lecrubier, 2006).

Three double-blind RCTs treating somatoform disorders were located. A 6 week multicentre RCT (n = 151) found that SJW extract (600 mg/day) was significantly superior to placebo in reducing somatoform symptoms as assessed via HAMA-SOM scale (Volz, Murck, Kasper, & Möller, 2002). A later double-blind RCT (n = 184) tested SJW extract in patients with somatization disorders. The results using six outcome measures demonstrated that 45.4% of the SJW group were classified as responders, compared with 20.9% who took placebo (Muller, Mannel, Murck, & Rahlfs, 2004).

A short-term 2 week study evaluated tablets containing 90 mg of Petasites hybridus (butterbur) in combination with Ze185: valerian 90 mg, passionflower 90 mg, and lemon balm 90 mg in patients with somatoform disorders (Melzer, Schrader, Brattstrom, Schellenberg, & Saller, 2009). One hundred eighty-two patients were randomized for a three-arm trial: Ze185 and butterbur versus Ze185 versus placebo. The four-herb combination was found to be significantly superior to the three-combination and placebo on a VAS and the BDI-II. All herbal combinations were found to be well-tolerated, with no serious adverse events.

5.5 | Attention-deficit hyperactivity disorder

ADHD is diagnosed by the DSM-V as a presentation at clinical levels of hyperactivity, impulsivity, and cognitive dysfunction related to inattention and impulsivity, occurring before the age of 12; these symptoms must be persistent and still be sufficient to cause significant personal and social distress (APA, 2013). A 4 week open label trial of 400mg/day American ginseng (Panax quinquefolium) plus 100 mg/day of ginkgo in 36 children with ADHD found that 74% improved significantly on Conner's ADHD scale, while having a 44% improvement on a social problems measure (Lyon et al., 2001).

Pycnogenol (an extract from French maritime pine bark) was also found to be superior to placebo after 4 weeks in a double-blind RCT involving 61 children with ADHD. On standardized measures and teacher and parent ratings, students on Pycnogenol had significantly greater improvements in hyperactivity, attention, concentration, and visual-motor coordination (Trebatická et al., 2006). The mechanisms of action for both Pycnogenol and ginkgo are considered to, in part, be mediated via antioxidant activity. In respect to nonsupportive data, a double-blind RCT found that ginkgo (80–120 mg/day) had no comparable benefit to methylphenidate in 50 children with ADHD (Salehi et al., 2010), whereas a high-profile robust 8 week double-blind RCT using 900 mg/day of SJW also found no benefits in the treatment of ADHD (Weber et al., 2008).

5.6 | Bipolar disorder I/II

Bipolar II disorder is characterized in the DSM-V as a condition whereby periods of MDD are accompanied by one or more hypomanic episodes, although in contrast, bipolar disorder I is diagnosed by the occurrence of one or more full-blown manic episodes with or without MDD (APA, 2013). Although herbal intervention in bipolar conditions may have a therapeutic role, it is currently recommended that these are studied and prescribed only as an adjunctive therapy with mood stabilizers in cases of pronounced mood oscillation (Currier & Trenton, 2002; Mohr, Pecenak, Svestka, Swingler, & Treuer, 2005).

It should be firstly noted that cases of herbal medicine-induced mania have been documented with SJW (Fahmi, Huang, & Schweitzer, 2002; Guzelcan, Scholte, Assies, & Becker, 2001; Nierenberg, Burt, Matthews, & Weiss, 1999; Stevinson & Ernst, 2004), Ma Huang (Ephedra sinica) (Boerth & Caley, 2003; Maglione, Miotto, Iguchi, Hilton, & Shekelle, 2005), ginkgo (Spinella & Eaton, 2002), and ginseng (type not specified; Vazquez & Aguera-Ortiz, 2002). High-dose SJW or concomitant pharmaceutical or recreational drugs were involved in most cases. Furthermore, causal links could not be established in these cases due to a lack of rechallenge with the herbal medicine involved. Although herbal-induced mania appears to occur idiosyncratically, monitoring is advised in cases of high-dosage, with use in patients with known bipolar disorders.

To date, one study has been conducted using a plant medicine for bipolar disorder, a clinical trial using ashwagandha. Sixty euthymic subjects with DSM-IV bipolar disorder were enrolled in an 8 week, double-blind RCT of ashwagandha (500 mg/day) as a "procognitive" agent added adjunctively to the medications being used as maintenance treatment for bipolar disorder (Chengappa et al., 2013). Cognitive testing at baseline and 8 weeks was assessed as the primary efficacy outcome. On the secondary outcomes of mood and anxiety scales, no significant difference between groups was found (however, it should be noted that participants were euthymic at the commencement of the study). Compared with placebo, ashwagandha provided significant benefits for three cognitive tasks: digit span backward, Flanker neutral response time, and the social cognition response rating of the Penn Emotional Acuity Test.

5.7 | Schizophrenia

Schizophrenia and related psychoses are serious mental disorders with a profound impact on cognition, emotion, and behaviour, and include symptoms such as hallucinations, thought disorder, and delusions (APA, 2013). Adjuvant prescription of ginkgo to antipsychotics in chronic schizophrenia treatment was evaluated via meta-analysis. Eight double-blind RCTs involving 1,033 patients were assessed (Chen, Hong, & Zheng, 2015). The result showed that ginkgo had a significant difference in ameliorating total and negative symptoms of chronic schizophrenia as an adjuvant therapy to antipsychotics, this is potentially due to the antioxidant effects. No significant between-group adverse effects were revealed; however, a reduction of extrapyramidal side effects was not evident across the ginkgo cohort. The authors note that all of these eight trials were carried out in China, and further transcultural research is needed.

A proprietary standardized American ginseng extract (HT1001) was assessed in a 4 week double-blind RCT involving 64 individuals with DSM-IV diagnosed schizophrenia (Chen & Hui, 2012). The primary outcome was assessment of cognitive effects. Results revealed

that visual working memory was significantly improved in the American ginseng group, but not in the placebo group. Furthermore, extrapyramidal symptoms were significantly reduced after 4 weeks treatment, compared with the placebo group. The mechanism of action underpinning these effects is currently not entirely known; however, anxiolytic effects have been revealed in animal models (Wei, Yang, Wang, & Wu, 2007).

6 | DISCUSSION

The current updated review revealed 24 herbal medicines for 11 psychiatric conditions; however, unlike the previous review that only uncovered a high standard of evidence existing for kava and SJW, further research has been conducted over the past decade giving weight to the use of saffron for depression and passionflower for anxiety. Other herbal medicines found to have encouraging evidence in the previous review and advised for further research were roseroot, scullcap, and *Zizyphus jujuba* (sour date seed). Although the first two have a couple of additional positive small-scale studies for depression and anxiety, respectively, larger studies are still required, and to date no double-blind RCTs have been conducted involving sour date seed. Recently studied plant medicines such as galphimia, turmeric, and ashwagandha also provide very encouraging evidence as additional therapeutic options for depressive and anxiety disorders and inspire the pursuit of researching more plant medicines with traditional usage for mental health conditions. Although MDD and GAD are still commonly researched in this field, study of herbal medicines in psychotic disorders, OCD, and ADHD has only grown marginally in the past decade. There is still a paucity of research in phobic, somatoform disorders, and currently none for panic disorder.

Outside of some European and Asian healthcare models, integration of psychotropic herbal medicines into conventional medical practice appears to still be some way off. In the past decade, no substantial advance has occurred in the development of new classes of synthetic antidepressant and anxiolytic medications, with SSRIs and benzodiazepines currently remaining first-line treatments in depression and anxiety disorders, respectively. However, as in the case of depression, a significant percentage of patients do not experience full remission with pharmaceutical treatments; thus additional treatment options are still needed. One potential option that is relatively unexplored is in the adjunctive co-prescribing of herbal medicines in combination with pharmaceuticals. In some herbal medicines, it is recognized that co-prescription may be unwise, for example, SJW with SSRIs due to potential serotonin syndrome and high-dose kava in combination with benzodiazepines due to a theoretical additive sedative effect. Regardless, co-prescription of certain herbal medicines with pharmaceuticals with complementary pharmacodynamic actions may in fact provide a beneficial synergistic effect (Borgert, Borgert, & Findley, 2005; Williamson, 2001). This also potentially allows for a lower dose of synthetic pharmaceuticals to be taken, thus reducing potential side effects. Regardless of this cautious application, to date, little study has occurred, aside from some isolated studies exploring augmentation of antidepressants. This remains an area of potential future study.

In conclusion, although evidence has grown in the past decade, there is still a need to conduct further robust double-blind RCTs for several herbal medicines with encouraging pilot data. There is also immense scope to explore different combinations of enhanced standardized preparations of these herbal medicines in the application for a wider range of psychiatric disorders.

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