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Plant-based Medicines (Phytoceuticals) in the Treatment of Psychiatric Disorders: A Meta-review of Meta-analyses of Randomized Controlled Trials

Les médicaments à base de plantes (phytoceutiques) dans le traitement des troubles psychiatriques: une méta-revue des méta-analyses d'essais randomisés contrôlés

Jerome Sarris, MHSc, PhD[1,2], Wolfgang Marx, BSc, MDietSt, PhD[3], Melanie M. Ashton, PhD[3], Chee H. Ng, MBBS, MMed (Psych), MD[2], Nicole Galvao-Coelho, PhD[1,4,5], Zahra Ayati, PharmD, PhD[1,6], Zhang-Jin Zhang, BMed, MMed, PhD[7,8], Siegfried Kasper, MD[9], Arun Ravindran, MD[10], Brian H. Harvey, BPharm, BSc Hons(Pharmacol), MSc, MD, PhD[11], Adrian Lopresti, PhD[12,13], David Mischoulon, MD, PhD[14], Jay Amsterdam, MD[15], Lakshmi N. Yatham, MBBS, MRCPsych, MBA (Exec)[16], and Michael Berk, MBBS, MMed(Psych), PhD[3,17,18]

Abstract

Objectives: Plant-based medicines have had a long-standing history of use in psychiatric disorders. Highly quantified and standardized extracts or isolates may be termed "phytoceuticals," in a similar way that medicinal nutrients are termed as

[1] Western Sydney University, NICM Health Research Institute, Westmead, Australia
[2] The Professorial Unit, The Melbourne Clinic; Department of Psychiatry, University of Melbourne, Melbourne, Australia
[3] Deakin University, IMPACT—the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia
[4] Postgraduate Program in Psychobiology and Department of Physiology and Behavior, Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil
[5] National Institute of Science and Technology in Translational Medicine, Brazil
[6] Division of Psychology and Mental Health, Department of Traditional Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[7] School of Chinese Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[8] Department of Chinese Medicine, The University of Hong Kong Shenzhen Hospital (HKU-SZH), Shenzhen, China
[9] Center for Brain Research, Medical University of Vienna, Spitalgasse, Wien, Austria
[10] University of Toronto and Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[11] Division of Pharmacology, Center of Excellence for Pharmaceutical Sciences, School of Pharmacy, North West University, Potchefstroom, South Africa
[12] College of Science, Health, Engineering and Education, Murdoch University, Perth, Australia
[13] Clinical Research Australia, Perth, Australia
[14] Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[15] Depression Research Unit, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[16] University of British Columbia, Vancouver, Canada
[17] Orygen, The National Centre of Excellence in Youth Mental Health, Centre for Youth Mental Health, Melbourne, Australia
[18] Florey Institute for Neuroscience and Mental Health and the Department of Psychiatry, The University of Melbourne, Melbourne, Australia

Corresponding Author:
Jerome Sarris, MHSc, PhD, Western Sydney University, NICM Health Research Institute Locked Bag 1797, Penrith, New South Wales 2751, Australia.
Email: j.sarris@westernsydney.edu.au

"nutraceuticals." Over the past 2 decades, several meta-analyses have examined the data for a range of plant-based medicines in the treatment of psychiatric disorders. The aim of this international project is to provide a "meta-review" of this top-tier evidence.

Methods: We identified, synthesized, and appraised all available up to date meta-analyses... of randomized controlled trials (RCTs) reporting on the efficacy and effectiveness of individual phytoceuticals across all major psychiatric disorders.

Results: Our systematic search identified 9 relevant meta-analyses of RCTs, with primary analyses including outcome data from 5,927 individuals. Supportive meta-analytic evidence was found for St John's wort for major depressive disorder (MDD); curcumin and saffron for MDD or depression symptoms, and ginkgo for total and negative symptoms in schizophrenia. Kava was not effective in treating diagnosed anxiety disorders. We also provide details on 22 traditional Chinese herbal medicine formulas' meta-analyses (primarily for depression studies), all of which revealed highly significant and large effect sizes. Their methodology, reporting, and potential publication bias were, however, of marked concern. The same caveat was noted for the curcumin, ginkgo, and saffron meta-analyses, which may also have significant publication bias.

Conclusions: More rigorous international studies are required to validate the efficacy of these phytoceuticals before treatment recommendations can be made. In conclusion, the breadth of data tentatively supports several phytoceuticals which may be effective for mental disorders alongside pharmaceutical, psychological therapies, and standard lifestyle recommendations.

Abrégé

Objectif : Les médicaments à base de plantes ont des antécédents de longue date d'utilisation dans les troubles psychiatriques. Des extraits ou isolats hautement quantifiés et normalisés peuvent porter le nom de « phytoceutiques », parallèlement aux nutriments médicinaux qui sont appelés « 'nutraceutiques ». Au cours des vingt dernières années, plusieurs méta-analyses ont examiné les données d'une série de médicaments à base de plantes dans le traitement des troubles psychiatriques. Ce projet international vise à offrir une « méta-revue » de ces données probantes de niveau supérieur.

Méthodes : Nous avons identifié, synthétisé et estimé toutes les méta-analyses disponibles d'essais randomisés contrôlés (ERC) portant sur l'efficience et l'efficacité des phytoceutiques individuels dans tous les principaux troubles psychiatriques.

Résultats : Notre recherche systématique a identifié 9 méta-analyses pertinentes d'ERC, les analyses primaires comportant les données des résultats de 5 927 personnes. Des données probantes méta-analytiques de soutien ont été trouvées pour le millepertuis dans le trouble dépressif majeur (TDM); la curcumine et le safran pour le TDM ou les symptômes dépressifs, et le ginkgo pour les symptômes totaux et négatifs de la schizophrénie. Le kava n'était pas efficace pour traiter les troubles anxieux diagnostiqués. Nous donnons aussi des détails sur 22 méta-analyses de formules de phytothérapie traditionnelles chinoises (surtout pour des études sur la dépression), qui ont toutes révélé des tailles d'effet très significatives et larges. Les biais de leur méthodologie, de leurs études et de leur publication éventuelle ont cependant soulevé des préoccupations. La même mise en garde a été notée pour les méta-analyses sur la curcumine, le ginkgo, et le safran, qui peuvent aussi présenter des biais de publication significatifs.

Conclusions : Des études internationales plus rigoureuses sont donc requises pour valider l'efficacité de ces phytoceutiques avant de pouvoir recommander des traitements. En conclusion, l'ampleur des données tente de refléter plusieurs phytoceutiques qui peuvent être efficaces pour les troubles mentaux avec la pharmacologie, les thérapies psychologiques et les recommandations usuelles de mode de vie.

Keywords

herbal medicine, Chinese herbal medicine, nutraceutical, mental disorders, depression, anxiety, clinical trials, psychiatry, mental health, treatment, schizophrenia, anxiety

Introduction

Data from the World Health Organization (WHO) reveal a continuing increase in the use of herbal and plant-based medicines, with an estimated 80% of the world population utilizing them as part of primary health care treatment for a range of physical ailments.[1] In the United States, a national household survey has shown that herbal/natural medicines, along with dietary supplements, were the most commonly utilized complementary therapies for psychiatric disorders, with St John's wort (*Hypericum perforatum* L.) and kava (*Piper methysticum*) as a treatment of mood disorders being the most used in this population.[2] This therapeutic approach is broadly under the umbrella of Traditional, Complementary, and Integrative Medicine as defined by the WHO.[3] The specific therapeutic application of natural products produced via pharmaceutical Good Manufacturing Practice, standardized and optimized, and in some cases purified (e.g., curcumin) or slightly modified (e.g., n-acetyl cysteine or 5-hydroxytryptophan) can be further subdivided into the terms "nutraceuticals"[4] and "phytoceuticals."

Phytoceuticals have a range of psychoactive effects that include putative antidepressant, anxiolytic, nootropic (cognitive enhancing), sedative, hypnotic, and analgesic properties.[5] The diverse mechanisms of action for these plant-based medicines primarily involve alteration of neurotransmitter synthesis and degradation, agonism and antagonism of neuroreceptors or inhibition of neurotransmitters reuptake proteins, or supporting the homeostatic function of the hypothalamic pituitary adrenal (HPA) axis.[5] For example, kava, through its main active compounds, kavalactones, acts as a γ-aminobutyric acid pathway agonist,[6] whereas St John's is a known monoamine reuptake inhibitor, although its modulation of HPA activity is also evident (note that preclinical data may not directly translate into pharmacodynamic effects at relevant human doses).[7] Further, phytoceuticals such as ginkgo (*Ginkgo biloba*) may exert antioxidant, anti-inflammatory, and antiplatelet activities, while increasing blood–brain barrier permeability, providing a potential adjunctive supportive treatment for brain disorders.[8] Traditional Chinese herbal medicine (TCHM) formulas are based on traditional medical knowledge, involving a range of different plant-based medicines often combined for both pharmacodynamic activity in addition to enhanced bioavailability (via the addition often of herbal "envoys" such as licorice root [*Glychrrhiza glabra*] and ginger rhizome [*Zingiber officinale*] to increase digestive absorption of the constituents).[9] Conventional mechanistic understandings of these agents in this context are, however, somewhat limited.

A recent review has examined the evidence of 23 plant-based medicines for 11 psychiatric disorders with human clinical trials; these include kava (*Piper methysticum*), passionflower (*Passiflora spp*) galphimia (*Galphimia glauca*), and chamomile (*Matricaria recutita*) for anxiety disorders; St John's wort (*Hypericum perforatum*), curcumin from turmeric (*Curcuma longa*), and saffron (*Crocus sativus*) for major depressive disorder (MDD); while ginkgo (*Ginkgo biloba*) was studied as an adjunctive treatment in schizophrenia.[10] However, an assessment of top-tier meta-analytic evidence via a "meta-synthesis" has not been conducted, and would provide far more definitive data. An example can be found in our sister-review on nutraceuticals,[11] which included 33 meta-analyses of placebo-controlled RCTs involving 10,951 individuals, covering a range of nutrients including ω-3 fatty acids, methylfolate, and n-acetyl cysteine.

The aim of this meta-review was to aggregate and evaluate the top-tier evidence for the efficacy of plant-based medicines in the treatment of psychiatric disorders. To achieve this, we identified, synthesized, and appraised all available data from meta-analyses of randomized controlled trials (RCTs) examining psychiatric outcomes for all phytoceuticals across various psychiatric disorders. Along with providing an overview of the efficacy of these agents across different disorders, we also aimed to explore which dosages and symptomatic targets were most appropriate in order to provide clinical guidelines.

Table 1. PICO (Participants, Interventions, Comparisons, Outcomes) Systematic Search Strategy.

Participants (any mental disorder)
Depression OR depressive OR mental illness* OR mental disorder* OR mood disorder* OR affective disorder* OR anxiety OR panic disorder OR obsessive compulsive OR ADHD OR attention deficit OR attentional deficit OR phobia OR bipolar type OR bipolar disorder* OR psychosis OR psychotic OR schizophr* OR antipsychotic* OR post traumatic* OR personality disorder* OR stress disorder* OR dissociative disorder*
Interventions (any nutrient or nutraceutical)
herbal OR herbal medicine OR plant medicine OR phytomedicine OR supplement OR st John's wort OR kava OR ginseng OR saffron OR curcumin OR valerian OR ginkgo OR rhodiola OR *Bacopa monniera* OR *Centella asiatica* OR *Cannabis* OR *Crocus sativus* OR *Curcuma longa* OR *Hypericum perforatum* OR *Galphimia* OR *Ginkgo biloba* OR *Lavandula* OR *Matricaria recutita* OR *Panax ginseng* OR *Passiflora incarnata* OR *Piper methysticum* OR *Rhodiola rosea* OR *Valeriana* OR *Withania somnifera*
Comparator (placebo controlled trials)
Random* OR placebo OR control* or adjunc* or clinical trial*
Outcomes (any from meta-analyses)
Meta-analy* OR metaanaly* OR meta reg* OR metareg* OR systematic review*

Methods

The search strategy and data synthesis were conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [6] and followed a preregistered protocol (PROSPERO: CRD42018105880).

Systematic Search

The title and key word search algorithm are presented in Table 1. The systematic search was conducted using Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment Database, Allied and Complementary Medicine, PsycINFO, and Ovid MEDLINE(R), from inception until January 2020.

A search of Google Scholar was conducted using the same key words to identify any additional relevant articles. Reference lists of included articles were also searched.

Eligibility Criteria

Eligibility criteria were organized in accordance with the PICO (Participants, Interventions, Comparisons, Outcomes) reporting structure, as described above.

Participants. We included studies of individuals with common and severe mental disorders: These included depressive disorders (including any clinical depression, diagnosed MDD or bipolar disorder (or mania), depression in pregnancy, in old age, or as a comorbidity to chronic health conditions); all diagnosed anxiety disorders; schizophrenia (examining total symptoms along with positive, negative, general symptoms, and tardive dyskinesia); states at risk for psychosis (examining attenuated psychotic

symptoms, negative symptoms, transition to psychosis, and functioning); and attention-deficit hyperactivity disorder.

All studies of the above conditions were eligible provided that at least 75% of the sample had a confirmed mental illness or at-risk state, ascertained by either clinical diagnostic history or reaching established thresholds on validated screening measures. Reports examining mental health outcomes in general population studies were only included if they met the above criteria. Studies examining neurodegenerative disorders (e.g., dementia) or neurodevelopmental disorders (e.g., autism, intellectual disability) were not included. It was decided via consensus that meta-analyses involving TCHMs would not be included in the main meta-synthesis analyses and forest plots due to concerns over continual highly significant findings ($P < 0.01$) or large effect sizes ($d > 0.8$). These studies were, however, included in tabular form to provide an overview of the results (and to illustrate the consistent positive findings and methodological concerns).

Interventions and comparisons. All plant-based interventions were considered for this meta-review, used either as adjunctive treatment or monotherapy. These could be either whole plant medicines or isolated constituents. Because this study aimed to provide a meta-review of top-tier evidence, only meta-analyses of RCTs were included.

Outcomes. All data on mental health outcomes (including changes in clinical measures, response rates) from meta-analyses of RCTs examining phytoceuticals for any eligible disorder were included in this meta-review. A meta-analysis was classified as eligible if: (a) it had clearly stated inclusion, intervention, and comparison criteria aligned with the participant, intervention, and comparison criteria listed above; (b) it reported a systematic search with a screening procedure; (c) it had used systematic data extraction and reported pooled continuous or categorical outcome data from more than one study.

Where overlapping meta-analyses of a given intervention for a specific outcome/disorder existed, the most recently updated meta-analysis was used, provided it captured more than 75% of the trials in the earlier version. Where older meta-analyses presented unique findings, through inclusion of a greater number of studies or use of particular subgroup analyses, these data were used as secondary analyses for our meta-review.

Quality Assessment of Included Meta-analyses

The quality of eligible meta-analyses was assessed using "A Measurement Tool to Assess Systematic Reviews" Version 2 (AMSTAR-2).[12] This is an updated version of the original AMSTAR designed to better capture review quality and confidence in findings. AMSTAR-2 assesses 16 constructs, which all indicate the quality of a systematic review/meta-analysis.

Data Extraction and Analysis

For each study, we manually extracted effect size data as standardized mean differences (SMDs) with 95% confidence intervals compared to placebo conditions, along with the *P* value. Data were initially extracted by 2 authors (J.S. and W.M.) and then cross-checked for quality with duplicate data extraction by an additional author (M.A.).

In line with conventional interpretations, SMDs were classified as negligible (<0.2), small (0.2 to 0.4), medium (0.4 to 0.8), or large (>0.8). In cases where continuous outcomes were reported as weighted mean differences or raw mean differences, these were recalculated into an SMD (Hedges' g) using Comprehensive Meta-Analysis 3.0. The SMDs were also adjusted in a uniform direction to indicate whether the intervention was either a positive or negative (in relation to placebo). Where meta-analyses had applied fixed-effects models to calculate the effect size of the phytoceutical compared to placebo, these were also recalculated using a random-effects model, such that SMDs across supplements/disorders could be meaningfully compared.

For both primary and secondary analyses, we also extracted the number of participants (*N*), along with the number of trials/comparisons (*n*) from which the pooled effect size was derived. Additionally, heterogeneity was quantified using the I^2 statistic and categorized as low ($I^2 < 25\%$), moderate ($I^2 = 25\%$ to 50%), or high ($I^2 > 50\%$). Where reported, all relevant study characteristics were also extracted, specifically with regard to the phytoceutical used (including formulation and dose), the sample and the diagnostic details, and any relevant subgroup analyses. The potential impact of publication bias was assessed when sufficient data for appropriate analyses were available.

Results

Systematic Search Results

The search revealed 882 results. Title and abstract screening removed 527 articles, with 103 being articles reviewed in full by the 3 reviewing academics (Figure 1). Of these, 72 were ineligible. Thus, in total, eligible data from 9 independent main meta-analyses of RCTs of plant-based medicines, and 22 TCHM formulas for the treatment of psychiatric disorders were included for this meta-review (Table 2).

Meta-analyses of RCTs with primary analyses including outcome data revealed 5 plant-based medicines focusing on 4 disorders. These were St John's wort for MDD[13] and curcumin for MDD or depression symptoms,[14,15] saffron for MDD or depression/anxiety symptoms,[16] kava for anxiety disorders,[17,18] and ginkgo for total and negative symptoms in schizophrenia (in addition to effects on tardive dyskinesia).[19–21] The total sample consisted of 5,927 individuals. Meta-analyses were typically based on monotherapy interventions administered in conjunction with "usual care" (without specifying treatment regimens) or as an adjunctive treatment to a specific class of psychotropics (e.g., selective serotonin reuptake inhibitors in depression or antipsychotics in schizophrenia). See below for details on TCHM formula study characteristics and outcome data.

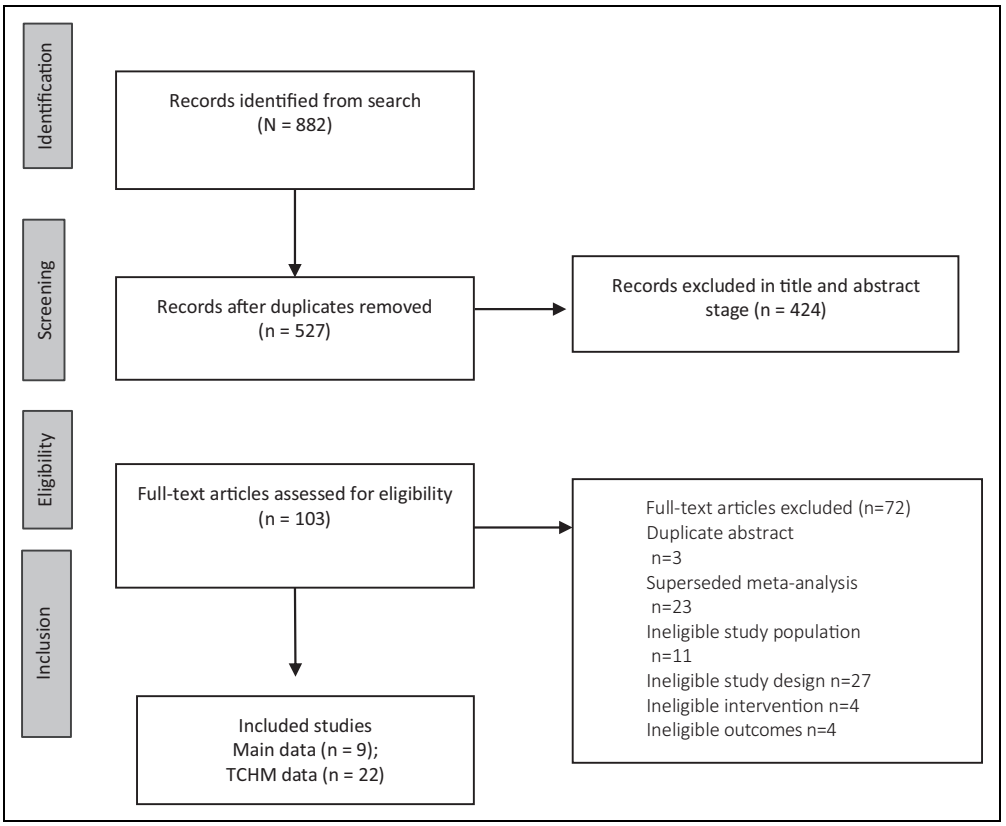

Figure 1. PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TCHM = traditional Chinese herbal medicine.

Quality Assessment of the Included Meta-analyses

The quality assessment of the data revealed that the individual meta-analyses fulfilled between 8 and 28 of the AMSTAR-2 criteria (median: 21, mean: 21.6). A qualitative assessment of the studies contained within the individual meta-analyses showed that all were RCTs (meeting our inclusion criteria); see Figure 2. A preponderance of the research was conducted in the United States and Europe for St John's wort, Europe and Australia for kava, Iran for saffron, China for ginkgo, and a range of countries for curcumin.

Efficacy and Effectiveness Data

Depression. Figure 2 shows the meta-review forest plot. St John's wort studies revealed a significant reduction of depressive symptoms in MDD compared to placebo ($N = 16$, SMD = 0.49, 0.23 to 0.74, $P < 0.05$; $I^2 = 89\%$).[13] Preparations studied varied, having differing levels of hypericin and hyperforin (typically 900 mg per day divided into 2 or 3 doses). As noted by the I^2 value, there was obvious high heterogeneity in data. Trials were mainly conducted in Europe and the United States, with study lengths between 6 and 8 weeks, while sample sizes were between 30 and 570. In respect to saffron, a significant reduction in depressive symptoms was found ($N = 14$, SMD = 0.99, 0.61 to 1.37, $P < 0.001$; $I^2 = 82\%$),[16] while once again, significant data heterogeneity was revealed. Saffron preparations studied were commonly standardized to crocin, or for one particular product to lepticrosalides® (a nonspecific measurement of bioactive compounds present in saffron, including safranal and crocin isomers). Trials were predominantly conducted in Iran, with study lengths between 4 and 8 weeks, while sample sizes ranged between 30 and 68. A positive finding was also revealed in support of curcumin for all studies included which assessed depressive symptoms ($N = 6$, SMD = 0.34, 0.13 to 0.56, $P = 0.002$; $I^2 = 0\%$).[15] Two meta-analyses are included in the meta-review due to differing subsample data ($n = 377$ and $n = 342$); however, both had similar effect sizes, and heterogeneity was very low. Sample sizes were between 30 and 111, with trial lengths between 4 and 8 weeks using 500 mg to 1 g of curcumin (commonly 1 g of curcumin per day), with the addition of piperine or prepared via a formulation designed to enhance bioavailability. These phytoceuticals were considered to have a good safety profile, although St John's wort has some clinical considerations regarding potential drug interactions, and certain potential adverse effects (see Table 2 for details).

Anxiety. The only plant-based medicines with meta-analytic evidence were kava and saffron. In respect to kava's anxiolytic effect, the most recent data suggest an absence of statistical significance for the treatment of a mixture of anxiety disorders (and in particular for GAD; $N = 4$, SMD = −0.02, −0.19 to 0.16, $P = 0.059$; $I^2 = 80\%$).[18] The data displayed marked

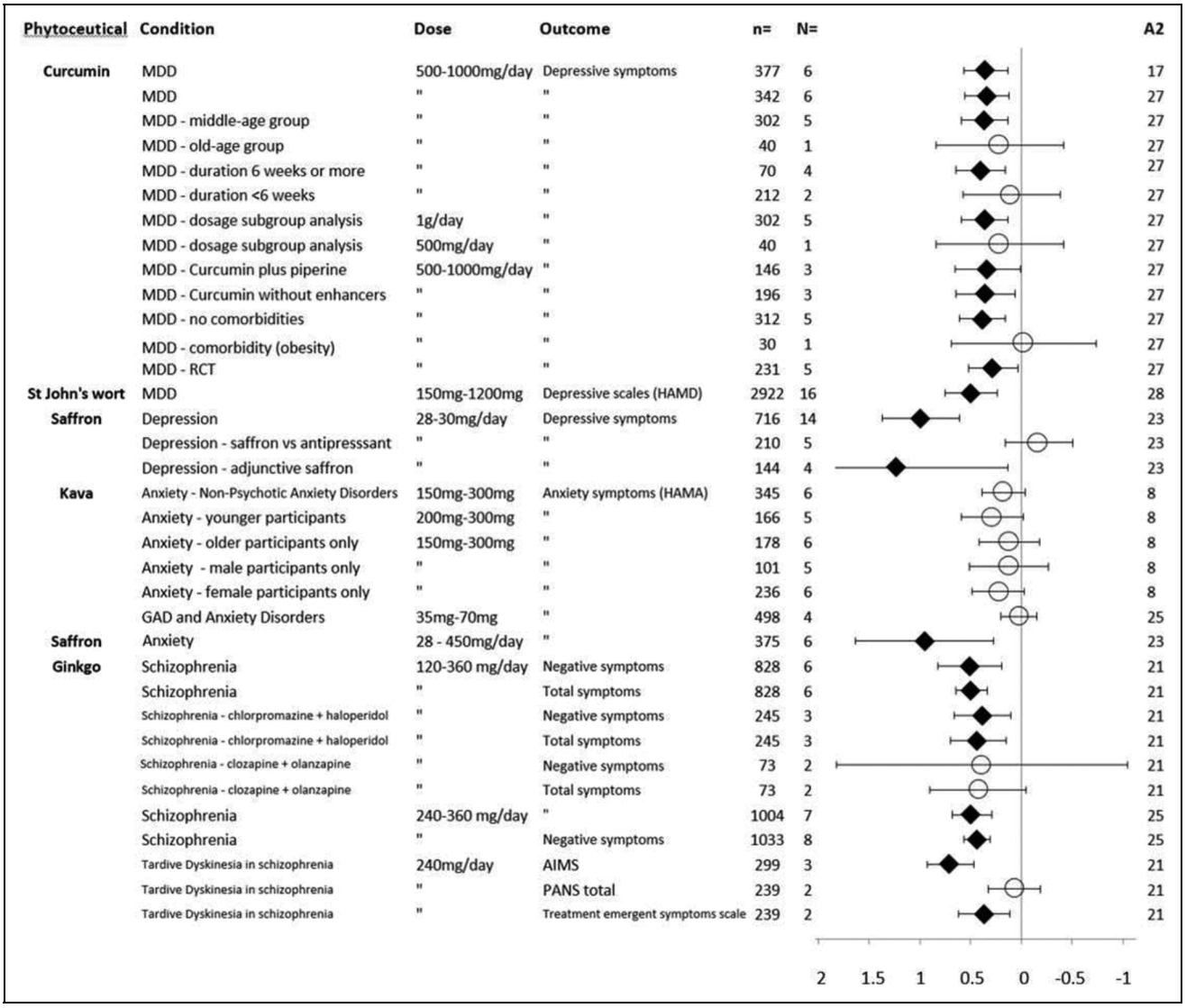

Figure 2. Effects of phytoceuticals in psychiatric disorders, shown as standardized mean difference with 95% CI. Circles represent no significant difference from placebo; diamonds represent *P* 0.05 compared to placebo; A2 = AMSTAR-2 total score; CI, confidence interval; GAD = generalized anxiety disorder; MDD = major depressive disorder.

heterogeneity. Trial lengths varied between 3 and 8 weeks with sample sizes between 35 and 100, and study extracts were standardized between 35 and 240 mg of kavalactones per day. An older meta-analysis of a specific kava extract (WS1490) also revealed a trend toward significance for treatment of a mixture of diagnosed anxiety disorders ($N = 6$, 0.18, −0.03 to 0.40, $P = 0.07$; I^2 = not available).[22] Study lengths were between 4 and 28 weeks, sample sizes ranged from 40 to 100 participants, and used 150 mg or 300 mg per day of the WS1490 kava extract. No significant finding was revealed when subgroup analyses were performed based on age (older/younger) or gender (male or female; *P* values all >0.05, see Figure 2). While studies revealed no major instance of adverse effects, some previous concerns have been noted over certain extracts having a negative effect on the liver (see Table 2 for details). A meta-analysis concerning saffron for anxiety outcomes revealed a significant effect in favor of the plant medicine over placebo ($N = 6$, SMD = 0.95, 0.27 to 1.63, $P = 0.006$; $I^2 = 89\%$).[16]

Schizophrenia. Three meta-analyses involving ginkgo providing data sufficiently unique to meet inclusion criteria. The most recent data showed that adjunctive use of ginkgo was superior to placebo in reducing total and negative symptoms of schizophrenia ($N = 7$, SMD = 0.49, 0.30 to 0.69, $P < 0.001$; $I^2 = 42\%$ and $N = 8$, SMD = 0.44, 0.32 to 0.57, $P < 0.001$; $I^2 = 0\%$, respectively[20]). It should be noted that meta-analytic data were not available assessing positive symptoms. As indicated via the I^2 scores, absent to moderate statistical heterogeneity was revealed. An older meta-analysis containing additional studies also supported ginkgo for both total and negative symptoms with an SMD in both cases of 0.5 in 6 studies (0.18 to 0.81, $P < 0.05$; $I^2 = 67\%$ and 0.36 to 0.64, $P < 0.05$; $I^2 = 7\%$, respectively).[19] Further separate subanalyses of adjunctive treatment

Table 2. Key Evidence Summaries for Plant-based Medicines.

Treatment	Key findings	Indicated usage	Comment
St John's wort	Superior efficacy to placebo and equivalency with antidepressants	MDD	• Studies employed standardized high-grade extracts (however efficacy was found regardless of whether standardized to hyperforin or hypericin). • Avoid high-hyperforin formulas if comedicating (may increase drug clearance via 3A4 and Pgp pathway induction)
Saffron	Superior efficacy to placebo and equivalency with antidepressants	MDD	• Encouraging evidence however further international studies are required to validate current findings from Iran • Stigma extracts are expensive, and quality control is vital
Curcumin	Superior efficacy to placebo	MDD	• Preliminary supportive data, however larger multicenter studies in well-defined MDD samples are now required • Clinicians are advised to utilize formulations which have sufficient bioavailability due to issues with curcuminoids not being readily absorbed via the intestinal lumen
Kava	Not effective in GAD, effective in reducing anxiety symptoms	Generalized non-GAD anxiety	• The current weight of evidence does not support its use in GAD and clinically diagnosed anxiety disorders, although there is potential use in reducing general symptoms of anxiety • Standardization to known kavalactone levels and use of high-quality kava stock from "noble" cultivars are critical to ensure quality • Avoid coadministration with alcohol or benzodiazepines, and caution in people with liver issues
Ginkgo	Superior efficacy to placebo in reducing total and negative scores in schizophrenia	Schizophrenia	• Preliminary supportive data, however larger multicenter studies in well-defined samples are now required • May have a use due to antioxidant properties in ameliorating extrapyramidal side effects
TCHM formulas	Superior efficacy to placebo and equivalence in some cases to medications for depression and schizophrenia	MDD, Schizophrenia	• Potentially effective for use in MDD or schizophrenia (not for treating positive symptoms specifically), however strong caution is advised to not overinterpret the consistently positive findings

Note. GAD = generalized anxiety disorder; MDD = major depressive disorder; Pgp = P glycoprotein pump; RCT = randomized controlled trial; TCHM = traditional Chinese herbal medicine.

of ginkgo with chlorpromazine and haloperidol, and also clozapine and olanzapine, revealed a significant effect over placebo. Finally, a separate meta-analysis revealed mixed evidence for use of ginkgo in treating tardive dyskinesia, assessed via the Abnormal Involuntary Movements Scale ($N = 3$, SMD = 0.70, 0.47 to 0.93, $P < 0.001$; $I^2 = 0\%$), Positive and Negative Syndrome Scale ($N = 2$, SMD = −0.06, 0.20 to −0.31, $P = 0.67$; $I^2 = 62\%$), and the Treatment Emergent Symptoms Scale ($N = 2$, SMD = 0.37, 0.16 to 0.63, $P = 0.004$; $I^2 = 0\%$).[21] The ginkgo studies in the meta-analyses used 120 to 360 mg of the standardized "EGb" extract. Study lengths were between 8 and 16 weeks, and sample sizes ranged from 29 to 568 participants. Ginkgo is generally regarded as a safe phytoceutical, although caution can be extended for couse with anticoagulants and prior to surgery due to mild anticoagulant effects.

Traditional Chinese herbal medicine formulas. A total of 22 meta-analyses were revealed via our search criteria concerning TCHMs for the treatment of depressive disorders ($N = 20$) and schizophrenia ($N = 2$; see Table 3). The number of studies included in the meta-analyses ranged from 7 to as many as 296 individual studies. The formulas studied included Chaihu-Shugan-San, Xiao Yao San, Ganmai Dazao, Wuling, Shuganjieyu, Wendan Decoction, Jiu Wei Zhen Xin (see supplementary Table 1). These were administered via decoction, granule, or capsule delivery. As mentioned in the Methods section, only the broad results were highlighted due to concerns over the reporting and methodological strengths of the studies included in the meta-analyses. All publications reported highly significant results in favor of the Chinese herbal medicine, and in some cases TCHMs were superior to standard antidepressants such as fluoxetine. Adverse events from these interventions were reported as very low, and in many adjunctive studies the Chinese herbal formulas were reported incidentally to ameliorate some of the medication side effects.

Table 3. Traditional Chinese Herbal Medicines.

Study	Title	Number of studies included (*n*)	Results
[23]	Meta-analysis of the clinical effectiveness of traditional Chinese medicine formula Chaihu-Shugan-San (CSS) in depression	10	"CSS in combination with antidepressant drugs treatment significantly improved depressive symptoms and significantly increased effective rate and recovery rate compared with antidepressant drugs therapy. In addition, the efficacy of CSS as a monotherapy was significantly better than antidepressants in improving depressive symptoms and increasing effective rate and was comparable to increasing recovery rate."
[24]	Chinese herbal formula Xiao Yao San for treatment of depression: A systematic review of randomized controlled trials	26	"Xiaoyaosan combined with antidepressants was more effective in comprehensive effect, the score of HAMD…compared with antidepressants alone. Xiaoyaosan was superior to antidepressants for the score of HAMD. However, Xiaoyaosan was not different from placebo for the score. There were no adverse effects reported in the trials from Xiaoyaosan."
[25]	Herbal medicine (Gan Mai Da Zao decoction; GMDZ) for depression: A systematic review and meta-analysis of randomized controlled trials	13	"GMDZ decoction produced better response rates than anti-depressants in post-stroke depression. One trial failed to show any beneficial effects of GMDZ decoction on response rate or HAMD score in depression in an elderly sample. Two trials tested GMDZ decoction in combination with anti-depressants but failed to show effects on response rate in major depression, while another did show beneficial effects on response rate in post-stroke depression."
[26]	Meta-analysis of Chinese herbal Xiaoyao (XYF) formula as an adjuvant treatment in relieving depression in Chinese patients	10	"XYF plus antidepressants reduced the HAMD scores compared with antidepressants alone in a random effect model. In subgroup analysis, XYF plus antidepressants reduced weighted mean difference was not observed in the treatment duration less than 8 weeks' subgroup and XYF powder subgroup. The adverse events included hyperhidrosis, dry mouth, nausea, and constipation. No serious adverse events were reported in any of the included trials."
[27]	Effectiveness and safety of Wuling capsule for post-stroke depression (PSD): A systematic review	16	"Wuling capsule used alone or integrated with conventional treatment was effective for PSD in terms of HAMD scores, response rate and with less adverse effects, of which, HAMD scores decreased significantly in favor of Wuling capsule from onset time to 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks and overall effect."
[28]	A systematic review on the efficacy, safety, and types of Chinese herbal medicine (CHM) for depression	296	"CHM monotherapy was better than placebo and as effective as antidepressants in reducing HDRS score. CHM were associated with less adverse events than antidepressants, and adding CHM to antidepressants reduced adverse events."
[29]	A meta-analysis of the efficacy and safety of traditional Chinese medicine formula GMDZ for depression	10	"GMDZ was significantly more efficacious than antidepressants in effective rate, but comparable in HDRS score. With GMDZ plus antidepressants with antidepressants alone, there was no significant difference in effective rate, but the end-point HDRS score was significantly lower in GMDZ antidepressants combination. Adverse events were more common with antidepressants than GMDZ and in antidepressants alone compared to GMDZ antidepressants combination."

(continued)

Table 3. (continued)

Study	Title	Number of studies included (*n*)	Results
[30]	Shuganjieyu capsule for major depressive disorder in adults: a systematic review	7	"Shuganjieyu capsule was superior than placebo in terms of response rate, remission rate, the scores of the mean change from baseline of the HAM-D17 and from baseline of traditional Chinese medicine (TCM) syndrome score scale scores. Shuganjieyu plus venlafaxine had a significantly higher response rate and was superior in terms of the scores of the mean change from baseline of the treatment emergent symptoms scale scores than venlafaxine alone."
[31]	Systematic review of traditional Chinese medicine for depression in Parkinson disease	10	"TCM combined with conventional drugs significantly improved the total scores of the unified Parkinson's disease rating scale and the score of the Hamilton rating scale for depression (HAM-D) compared with conventional drug, respectively."
[32]	Comparison between herbal medicine and fluoxetine for depression: A systematic review of randomized controlled trials	26	"The results achieved weak evidence which showed CHM had similar effect to fluoxetine (20 mg/day) on relieving depression according to HAMD assessment, but fewer incidences of adverse events than the drug. No serious adverse event was found in neither CHM nor fluoxetine group."
[33]	Wendan decoction (WDD) for treatment of schizophrenia: A systematic review of randomized controlled trials	13	"WDD combined with antipsychotic drugs were more effective in clinical comprehensive effect, Positive and Negative Syndrome Scale (PANSS) scores and Brief Psychiatric Rating Scale scores compared with antipsychotic drugs alone. However, WDD had less effectiveness compared with antipsychotics in clinical comprehensive effect; and WDD was not different from antipsychotic drugs for PANSS scores. The side effects were significantly reduced in the intervention group compared with the control group."
[34]	Systematic review on randomized controlled trials of coronary heart disease complicated with depression treated with Chinese herbal medicines	13	"CHMs showed no statistic difference in the 4th week but it was associated with a statistically significant difference in the 8th week. CHMs together with antidepressants showed significant statistic differences both in the 4th week and in the 8th week."
[35]	Wuling capsule for major depressive disorder: A meta-analysis of randomized controlled trials	12	"No significant differences between the Wuling capsule alone and antidepressant monotherapy. The Wuling capsule–antidepressant co treatment was superior to antidepressant monotherapy in symptomatic improvement at last-observation endpoint as well as study-defined response and remission. Wuling capsule was associated with fewer adverse drug reactions than antidepressant monotherapy."
[36]	Is the Chinese medicinal formula Guipi decoction (GPD) effective as an adjunctive treatment for depression? A meta-analysis of randomized controlled trials	9	"Compared with antidepressant therapy alone, treatment with a combination of GPD and an antidepressant significantly improved the symptoms of depression and increased the rates of effectiveness as well as recovery. The adverse effects of GPD were not found to be significant in these studies."

(continued)

Table 3. (continued)

Study	Title	Number of studies included (*n*)	Results
[37]	Efficacy and safety of Xiaoyao formula (XYF) as an adjuvant treatment for post-stroke depression: a meta-analysis	7	"Adjuvant treatment with XYF had additional benefits in terms of improved total response rates, reduced Hamilton's depressive scale and decreased Scandinavian Stroke Scale. No serious adverse events were observed in any of the included trials."
[38]	Treatment of depression with Chai Hu ShuGan San: a systematic review and meta-analysis of 42 randomized controlled trials	42	"Meta analyses showed better effect of Chai Hu Shu Gan San than fluoxetine for pure depression, for post-stroke depression, and for postpartum depression. None of the articles reported severe adverse events of oral administration of Chai Hu Shu Gan San. Any adverse effects of using Chai Hu Shu Gan San alone were fewer than those of regular Western medicines."
[39]	Adjuvant therapy of Oral Chinese Herbal Medicine (OCHM) for menopausal depression: A systematic review and meta-analysis	22	"Adjuvant therapy of OCHM was effective in reducing HAMD scores compared to pharmacotherapy. OCHM adjuvant therapy for menopausal depression was superior to pharmacotherapy in terms of response rate of reducing HAMD scores."
[40]	Efficacy and safety of a formulated herbal Granula, Jiu Wei Zhen Xin (JWZXG), for generalized anxiety disorder: A meta-analysis	14	"No significant difference in response rate and no significant difference between JWZXG group and azapirones group in rate of adverse events. Though no difference exists between JWZXG group and azapirones group in HAMA total score from baseline, JWZXG group was inferior to selective serotonin reuptake inhibitors (SSRIs) group which had more adverse events than JWZXG group."
[41]	Effectiveness of traditional Chinese medicine as an adjunct therapy for refractory schizophrenia: A systematic review and meta-analysis	14	"TCM was observed to have beneficial effects on aspects of the Positive and Negative Syndrome Scale (PANSS) including total score changes and negative score changes, as well as clinical effects estimated with PANSS or the Brief Psychiatric Rating Scale (BPRS). The changes in extrapyramidal side effects (RSESE) scores from baseline to the end of the treatment period were similar in two groups of related trials. TCM was also reported to mitigate some anti-psychotic related side-effects and overall, TCM adjuvant therapy was generally safe and well tolerated."
[42]	Twelve Chinese herbal preparations for the treatment of depression or depressive symptoms in cancer patients: a systematic review and meta-analysis of randomized controlled trials	18	"Twelve different types of Chinese herbal preparations showed a better therapeutic effect in most comparisons when measured in terms of depression rating scale scores, or when measured in terms of treatment response rate. Compared with antidepressants, these CHMs showed borderline superiority for improving the response rate. Subgroup analysis based on psychiatric diagnosis did not modify the direction of these estimates and neither could it explain the high level of heterogeneity."
[43]	Oral Chinese Herbal Medicine for depressive disorder in patients after percutaneous coronary intervention: A systematic review and meta-analysis	16	"When compared with antidepressants alone, CHMs showed similar benefits with less side effects, meanwhile, the combination therapy may have more advantages than antidepressants alone. When identified with placebo, CHMs seem to have more advantages in relieving depressive symptoms. However, when compared with basic treatment of post-PCI, CHMs showed different results in two trials."

Discussion

This meta-review aggregated and evaluated all the recent top-tier evidence from meta-analyses of RCTs examining the efficacy of plant-based medicines for psychiatric disorder symptoms. We identified 9 eligible meta-analyses published from 2005 onward with primary analyses including 5,927 individuals with psychiatric disorders randomized to individual plant-based medicines or placebo control conditions. For a narrative summary of results and clinical considerations, see Table 3.

The interventions with the strongest evidentiary support were for St John's wort for MDD (supported also by pooled analysis of key European study data[43]), curcumin, and saffron for MDD and depression symptoms, and ginkgo for total and negative symptoms. Kava was not effective in treating diagnosed anxiety disorders, with an absence of statistical significance in GAD, while some supportive data for saffron for this application were evident. These results in the main reflects the position held in the most recent Canadian Network for Mood and Anxiety Treatment guidelines.[44] The data concerning kava should also be further taken into context due to a recently published large RCT involving the phytoceutical in the treatment of GAD, which revealed a nonsignificant effect compared to placebo[45] on the Hamilton Anxiety Rating Scale. However, it can be noted that research has generally supported kava in nonclinical populations (potentially for more "situational" anxiety as a short-term anxiolytic). All 22 meta-analyses of Chinese herbal medicine formulas (primarily for depression studies) revealed highly significant and large effect sizes, but their methodologies, reporting, and potential publication bias were of marked concern. Additionally, an important caveat is that many studies included in the curcumin, ginkgo, and saffron meta-analyses may have had publication bias (in respect to negative studies potentially not being published). Additional more rigorous international studies are therefore required to validate these results.

While many strengths of this meta-review are evident, including the collation of tier-1 meta-analytic RCT data via a rigorous systematic search process, some limitations are noted. First, studies were confined to the English language, and some research may have been excluded. Further, some of the data from studies contained within the individual meta-analyses had poor reporting and weak methodological standards, small samples, or absence of constituent standardization, thus some degree of caution needs to be applied, most notably in respect to TCHM formulas[46] and saffron. A final consideration is that regarding the data including within the meta-analyses, these commonly derived data from individual RCTs using "completer" analyses, and not more statistically acceptable intention-to-treat data. Due to this, there is presently limited clinical utility of the results in the meta-review in making treatment determinations. More research is required to firmly validate TCHM formulas and saffron across more diverse jurisdictions, in addition to more research on more newly studied phytoceuticals such as curcumin.

We also note that other plant medicines for certain psychiatric disorders with supportive or mixed RCT evidence exist that have not been subjected to meta-analysis, in particular for other disorders such as bipolar depression. These include for affective disorders: lavender (*Lavandula spp.*), roseroot (*Rhodiola rosea*), catmint (*Nepeta menthoides*), dodder (*Cuscuta spp.*), Galphimia (*Galphimia glauca*), chamomile (*Matricaria recutita)*, passionflower (*Passiflora incarnata*), ginkgo (*Ginkgo biloba*), ashwagandha (*Withania somnifera*; also revealing procognitive effects in bipolar disorder), and mangosteen (*Garcinia mangostana*) for schizophrenia and mood disorders.[10] Isolated RCTs have also been conducted for St John's wort in the treatment of social phobia and obsessive compulsive disorder (OCD) and somatoform (all *NS*), with other positive yet less convincing data for valerian (*Valeriana officinalis*) or milk thistle (*Silybum marianum*) in OCD[10]; while there are promising mood-modulating candidates such as kanna (*Sceletium tortuosum*)[47–49] and a standardized lavender oil, Silexan.[50] Although these data are encouraging, further replicated research of these are needed in order to subject them to meta-analysis.

In conclusion, this "meta-synthesis" of the data from 9 meta-analyses showed positive findings for a variety of plant-based medicines in a range of psychiatric disorders, albeit limited by the quality of source data. The breadth of data supports that several phytoceuticals may be an effective option for mental disorders, alongside pharmaceutical, psychology therapies, and standard lifestyle recommendations. Further robust RCTs across various jurisdictions are required to firmly validate these findings.

Authors' Note

Data access is not applicable to this meta-review.

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ORCID iDs

Jerome Sarris, MHSc, PhD https://orcid.org/0000-0001-9287-8854
Melanie M. Ashton, PhD https://orcid.org/0000-0001-6832-4157
Arun Ravindran https://orcid.org/0000-0002-1655-2753
Michael Berk, MBBS, MMed(Psychiatry), PhD https://orcid.org/0000-0002-5554-6946

Supplemental Material

Supplemental material for this article is available online.

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