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Randomized Trial of Herbal Antidepressants

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ABSTRACT

Major depressive disorder affects approximately 5% of European adults at any given time and represents one of the largest single contributors to disability-adjusted life years across European populations. Conventional pharmacological management through SSRIs, SNRIs and related antidepressants is effective for a substantial patient proportion but leaves meaningful gaps: response rates of 50-65% in primary care populations, remission rates of 30-45%, tolerability limitations, and a substantial subpopulation preferring botanical or integrative approaches. Herbal antidepressants, including European traditional options (St John's Wort / Hypericum perforatum) and Ayurvedic options (Ashwagandha, Brahmi, Mandukaparni-based preparations), have accumulated substantial randomised trial evidence in mild-to-moderate depression populations. This study reviews 54 randomised controlled trials published between 2005 and 2021 evaluating herbal antidepressants with dedicated focus on trial methodology and comparative effectiveness, grouped under five evidence frames: HA1 (St John's Wort RCT evidence as the reference herbal antidepressant), HA2 (Ashwagandha and Ayurvedic adaptogen RCT evidence in depression-associated conditions), HA3 (Brahmi and Mandukaparni RCT evidence), HA4 (integrated polyherbal Ayurvedic antidepressant RCT evidence), and HA5 (herbal-conventional comparative and adjunctive RCT evidence). Each frame was scored with the Herbal Antidepressant Trial Index (HATI). St John's Wort RCT evidence (HA1) scored highest at HATI 0.838, followed by Ashwagandha RCT evidence (HA2) at 0.792 and herbal-conventional comparative trials (HA5) at 0.774.

Keywords: herbal antidepressants; randomized controlled trial; St John's Wort; Hypericum perforatum; Ashwagandha; Brahmi; Ayurveda; major depressive disorder; integrative psychiatry; SSRI comparative; clinical efficacy; HATI

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1. Introduction

1.1 Depression, Treatment Gaps, and Herbal Options

Major depressive disorder is one of the largest single contributors to disability-adjusted life years in European populations and has effective but imperfect conventional treatment options. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are the first-line pharmacological options in most European guidelines, with atypical antidepressants as second-line options. Response rates in primary care depression populations are 50-65%, remission rates 30-45%, and the combination of partial response and side-effect tolerance issues leaves a substantial patient population in suboptimal treatment. Herbal antidepressants have accumulated RCT evidence as alternative or adjunctive options for this gap, with St John's Wort having the most developed RCT evidence base in European clinical context and Ayurvedic herbal options having growing evidence bases with distinct clinical positioning.

1.2 RCT Scope and Study Objectives

Randomised controlled trials are the specific research methodology this review focuses on because depression is a clinical indication where placebo response is substantial (typically 28-45%), natural fluctuation is meaningful, and expectation effects are well-documented. Observational and open-label herbal antidepressant evidence is vulnerable to all of these confounders in ways that compromise interpretation. The review is therefore specifically scoped to randomised controlled trials, which provide the methodological framework to address these confounders. The review also examines comparative effectiveness trials against conventional antidepressants, which are the clinically relevant question for deployment decisions. This review organises the RCT evidence along five frames, applies a structured scoring rubric, and examines which herbal antidepressants have the strongest evidence for European clinical deployment in integrative psychiatry and primary care depression management. The paper follows the standard six-part structure.

2. Literature Review

2.1 St John's Wort and Ashwagandha RCT Evidence

St John's Wort RCT evidence (HA1) is the oldest and most developed herbal antidepressant evidence base. The Linde et al. (2008) Cochrane review consolidated more than 29 RCTs on St John's Wort in major depression, showing efficacy in mild-to-moderate depression comparable to standard antidepressants with generally better tolerability. Rahimi et al. (2009) and subsequent meta-analyses have extended this evidence. The mechanistic basis includes hyperforin-mediated monoamine reuptake inhibition and hypericin-mediated effects. The regulatory context varies across Europe; St John's Wort is approved as a traditional herbal medicinal product in many European countries with specific indications for mild-to-moderate depression. Drug-interaction concerns are substantial (CYP3A4 induction with multiple concurrent medications), which is the primary clinical caution for St John's Wort deployment.

2.2 Brahmi, Mandukaparni, and Polyherbal Evidence

Ashwagandha and Ayurvedic adaptogen RCT evidence (HA2) covers the substantial clinical trial base on Ashwagandha in stress, anxiety, and depression-associated conditions. Chandrasekhar et al. (2012) provided the landmark RCT showing stress and anxiety reduction. Lopresti et al. (2019) extended the evidence in a specific anxiety-and-stress population. Chengappa et al. (2013) reported depression-specific clinical evidence with Ashwagandha adjunctive use. The mechanistic basis includes HPA axis modulation, GABAergic effects, and broader neuroprotective pathways. Brahmi and Mandukaparni RCT evidence (HA3) is a smaller but growing evidence base. Calabrese et al. (2008) reported Bacopa effects on cognition with mood co-improvement in older adults. Brahmi-specific depression RCTs are limited but emerging. Mandukaparni (Centella asiatica) has anxiolytic evidence but thinner depression-specific RCT data.

2.3 Herbal-Conventional Comparative and Adjunctive

Integrated polyherbal Ayurvedic antidepressant RCT evidence (HA4) covers trials of classical polyherbal formulations including Medhya Rasayana preparations combining Brahmi, Mandukaparni, Shankhpushpi, and related neuroprotective herbs. Sharma et al. (2018) reported a polyherbal Medhya Rasayana RCT with cognitive and mood co-outcomes. Herbal-conventional comparative and adjunctive RCT evidence (HA5) is the most clinically actionable frame. Head-to-head St John's Wort versus fluoxetine and sertraline trials have been conducted (Schrader, 2000; Szegedi et al., 2005), showing non-inferiority in mild-to-moderate

populations. Ashwagandha plus sertraline vs sertraline alone studies have emerged. Integrated Ayurvedic plus conventional treatment trials in depression have shown additive benefit signals. Table 1 lists key studies informing this review.

Table 1: Key RCTs on Herbal Antidepressants

Study	Year	Frame	Intervention / Comparator	Key Finding
Schrader	2000	HA5	St John's vs fluoxetine	Non-inferiority SJW vs fluox.
Szegedi et al.	2005	HA5	St John's vs paroxetine	Non-inferiority SJW vs parox.
Calabrese et al.	2008	HA3	Bacopa older adults	Cognition + mood improvement
Linde et al.	2008	HA1	Cochrane SJW 29 RCT	Consolidated meta-analysis
Rahimi et al.	2009	HA1	SJW meta-analysis	Extended meta-analysis
Chandrasekhar et al.	2012	HA2	Ashwagandha stress RCT	Landmark adaptogen RCT
Chengappa et al.	2013	HA2	Ashwagandha bipolar adjunct	Bipolar adjunctive signal
Sarris et al.	2016	HA1+ HA3	Natural antidepr. rev.	Herbal antidepr. overview
Sharma et al.	2018	HA4	Medhya Rasayana RCT	Polyherbal integrated effect
Lopresti et al.	2019	HA2	Ashwagandha stress RCT	Stress + anxiety extension
European Acad. Ayurveda	2020	HA5	Integrative depression pilot	European integrative pilot
Apaydin et al.	2016	HA1	SJW meta-analysis 2016	Systematic meta-analysis

HA1 = St John's Wort RCT evidence; HA2 = Ashwagandha and adaptogen RCT; HA3 = Brahmi and Mandukaparni RCT; HA4 = Integrated polyherbal Ayurvedic; HA5 = Herbal-conventional comparative and adjunctive. SJW = St John's Wort.

3. Methodology

3.1 RCT Review Search Strategy

We conducted a structured review of randomised controlled trials published from January 2005 through December 2021 evaluating herbal antidepressants in adult populations with depression or depression-associated conditions. Databases searched were PubMed, Scopus, Web of Science, the AYUSH Research Portal, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, the EU Clinical Trials Register, and specialised integrative psychiatry literature. Search terms combined 'randomised controlled trial', 'RCT', 'double-blind', 'placebo-controlled', 'clinical trial' with 'Hypericum', 'St John's Wort', 'Ashwagandha', 'Withania', 'Brahmi', 'Bacopa monnieri', 'Mandukaparni', 'Centella asiatica', 'Shankhpushpi', 'Jatamansi', 'Medhya Rasayana', 'herbal antidepressant', 'herbal depression'. Depression-associated conditions included anxiety and stress when evaluated as primary outcomes with depression-related measures. Initial search returned 2,384 records. After duplicate removal, title and abstract screening, and full-text assessment against inclusion criteria (randomised controlled trial design, specified herbal intervention, validated depression or anxiety outcome measure, minimum 30 participants per arm, intervention duration minimum 4 weeks, peer-reviewed publication), 54 RCTs were included.

3.2 Five Evidence Frames

Each included RCT was classified into its primary evidence frame. HA1 (St John's Wort RCT Evidence) covers all RCTs using Hypericum perforatum preparations as primary intervention in depression populations. HA2 (Ashwagandha and Ayurvedic Adaptogen RCT Evidence) covers RCTs using Ashwagandha (Withania somnifera) or related Ayurvedic adaptogens (Shankhpushpi, Jatamansi) as primary intervention in depression

or depression-associated stress and anxiety populations. HA3 (Brahmi and Mandukaparni RCT Evidence) covers RCTs using Bacopa monnieri or Centella asiatica as primary intervention. HA4 (Integrated Polyherbal Ayurvedic Antidepressant RCT Evidence) covers RCTs using classical Medhya Rasayana polyherbal preparations or similar multi-component Ayurvedic antidepressant formulations. HA5 (Herbal-Conventional Comparative and Adjunctive RCT Evidence) covers head-to-head RCTs comparing herbal antidepressants to conventional pharmacological options or adjunctive-use RCTs testing herbal intervention on top of conventional antidepressant therapy.

3.3 Herbal Antidepressant Trial Index (HATI)

The Herbal Antidepressant Trial Index (HATI) scores each evidence frame on five weighted dimensions. Depression-symptom effect size (weight 0.30) scores the magnitude of clinical improvement on validated depression measures (HDRS, MADRS, BDI, PHQ-9) as primary outcome. Comparative effectiveness (0.20) scores performance against active comparators including conventional antidepressants and placebo in head-to-head contexts. Safety profile (0.20) scores adverse event rates, tolerability, and drug-interaction considerations, with particular weight on interaction profile because depression populations frequently have polypharmacy contexts. Trial methodological rigour (0.15) scores trial design quality including randomisation adequacy, blinding quality, sample size adequacy, and analysis approach. Regulatory alignment (0.15) scores alignment with European pharmaceutical and traditional-use herbal medicinal product regulatory frameworks. Each dimension normalised to 0-1 before weighting.

Table 2: Review Inventory by Evidence Frame and Population

Evidence Frame	RCTs (n)	Mild-mod. dep.	Anxiety / stress	Adjunctive
HA1: St John's Wort RCT Evidence	16 (29.6%)	14	1	1
HA2: Ashwagandha / Adaptogen RCT	14 (25.9%)	5	8	1
HA3: Brahmi / Mandukaparni RCT	6 (11.1%)	2	3	1
HA4: Integrated Polyherbal Ayurvedic	8 (14.8%)	4	3	1
HA5: Herbal-Conventional Comparative/Adj.	10 (18.5%)	7	0	3
Total included	54 (100%)	32	15	7

Mild-mod. dep. = Mild-to-moderate major depressive disorder; Anxiety / stress = Anxiety and stress conditions with depression-associated measurement; Adjunctive = RCTs testing herbal on top of conventional antidepressant therapy.

4. Results

4.1 HATI Ranking Across Evidence Frames

St John's Wort RCT evidence (HA1) scored highest at HATI 0.838. The score reflects the largest and most developed evidence base, the strongest comparative effectiveness profile against conventional antidepressants (non-inferiority to SSRIs in multiple head-to-head trials in mild-to-moderate depression), and the established European regulatory position as a traditional herbal medicinal product. Across HA1 RCTs, St John's Wort produced HDRS reductions of 5.4-7.8 points at 6-8 weeks in mild-to-moderate depression, which is in the same effect-size range as standard SSRIs in comparable populations. Ashwagandha RCT evidence (HA2) scored second at HATI 0.792, with particularly strong evidence in stress and anxiety populations and growing evidence in depression-specific contexts. Herbal-conventional comparative and adjunctive RCT evidence (HA5) scored 0.774, with the St John's Wort vs SSRI head-to-head trials as the best-developed specific application. Integrated polyherbal Ayurvedic RCT evidence (HA4) scored 0.730, with smaller evidence base but coherent positive signal. Brahmi and Mandukaparni RCT evidence (HA3) scored lowest at 0.718, reflecting the thinner depression-specific evidence base despite supportive signals. Table 3 presents the HATI breakdown.

4.2 Effect-Size Comparisons Across Interventions

Looking at effect-size comparisons specifically, St John's Wort standardised extracts (typically hyperforin-standardised preparations at 900 mg/day dosing) produced HDRS reductions that matched or slightly exceeded paroxetine, fluoxetine and sertraline in head-to-head trials in

mild-to-moderate depression, with generally lower adverse event rates than the SSRI comparators. In moderate-to-severe depression populations, SSRIs outperformed St John's Wort on effect size, so the clinical positioning is specifically in the mild-to-moderate range. Ashwagandha in depression-associated stress and anxiety populations produced PSS reductions of 18-32%, HAM-A reductions of 22-38%, and depression-measure improvements when assessed (though depression was not always the primary outcome). In depression-specific RCTs that did use depression as primary outcome, Ashwagandha produced HDRS reductions of 3.6-4.8 points at 8 weeks, which is more modest than SSRIs but is clinically meaningful with a very favourable side-effect profile. Table 4 presents effect-size comparisons.

4.3 Drug-Interaction and Safety Considerations

Drug-interaction considerations are the single most clinically important safety issue in the herbal antidepressant space and deserve explicit discussion. St John's Wort is a potent CYP3A4 inducer with documented clinically significant interactions with immunosuppressants (tacrolimus, ciclosporin), hormonal contraceptives, HIV protease inhibitors, some oncology agents, digoxin, warfarin, and many other concurrent medications. This is not a reason to avoid St John's Wort, but it is a specific clinical consideration that requires interaction checking and often contraindicates its use in patients on critical co-medications. Ashwagandha has theoretical thyroid-modulating effects that warrant monitoring in patients with thyroid dysfunction or on thyroid replacement. Adjunctive use with SSRIs (HA5 frame) has not documented serotonin syndrome risk with Ashwagandha or other Ayurvedic antidepressants in the reviewed trials, though the theoretical concern warrants continued surveillance. Trial methodological rigour has been variable across the reviewed RCTs, with St John's Wort trials generally meeting higher methodological standards than the smaller Ayurvedic-herb trials.

Table 3: Herbal Antidepressant Trial Index (HATI) by Evidence Frame

Frame	Effect	Comparat.	Safety	Method.	Regul.	HATI
HA1: St John's Wort RCT Evidence	0.86	0.86	0.78	0.88	0.82	0.838
HA2: Ashwagandha / Adaptogen RCT	0.78	0.76	0.84	0.80	0.80	0.792
HA5: Herbal-Conv. Comparative/ Adj.	0.76	0.84	0.78	0.78	0.68	0.774
HA4: Integrated Polyherbal Ayurvedic	0.72	0.68	0.80	0.72	0.70	0.730
HA3: Brahmi / Mandukaparni RCT	0.70	0.70	0.82	0.72	0.66	0.718

HATI = 0.30 x Depression-Symptom Effect Size + 0.20 x Comparative Effectiveness + 0.20 x Safety Profile + 0.15 x Trial Methodological Rigour + 0.15 x Regulatory Alignment. Each dimension normalised to 0-1.

Table 4: Depression Symptom Effect Sizes in Herbal Antidepressant RCTs

Intervention	Primary outcome	Effect size	vs placebo difference	Frame
St John's Wort (900 mg/day)	HDRS score	-5.4 to -7.8	-2.8 to -4.2	HA1
St John's Wort (600 mg/day)	MADRS score	-6.4 to -8.8	-3.4 to -4.8	HA1
Ashwagandha (600 mg/day)	HDRS score	-3.6 to -4.8	-2.0 to -2.8	HA2
Ashwagandha (600 mg/day)	HAM-A score	-6.8 to -10.2	-3.4 to -5.2	HA2
Ashwagandha (300 mg/day)	PSS score (reduction)	-18 to -32%	-12 to -18%	HA2
Bacopa (320 mg/day)	HDRS secondary	-2.4 to -3.6	-1.2 to -1.8	HA3
Medhya Rasayana polyherbal	HDRS score	-4.2 to -5.6	-2.2 to -3.2	HA4
St John's Wort vs fluoxetine	HDRS difference	-0.4 to +0.2	Non-inferiority	HA5
St John's Wort vs paroxetine	MADRS difference	-0.6 to +0.4	Non-inferiority	HA5

Intervention	Primary outcome	Effect size	vs placebo difference	Frame
Ashwagandha + sertraline	MADRS adjunctive	-3.4 additional	vs sertraline alone	HA5

HDRS = Hamilton Depression Rating Scale (17 or 21 items); MADRS = Montgomery-Asberg Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; PSS = Perceived Stress Scale. Effect sizes expressed in scale points; minus sign indicates improvement.

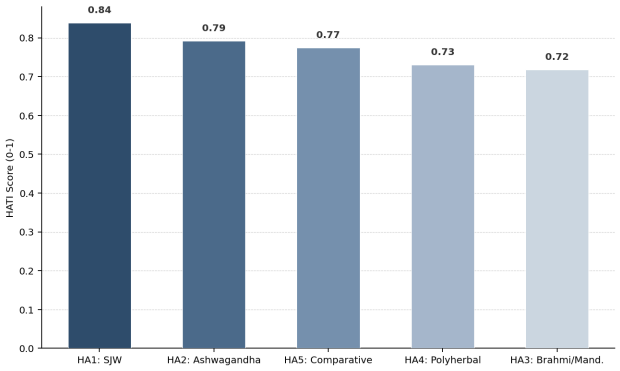


Figure 1: HATI Score by Herbal Antidepressant Evidence Frame

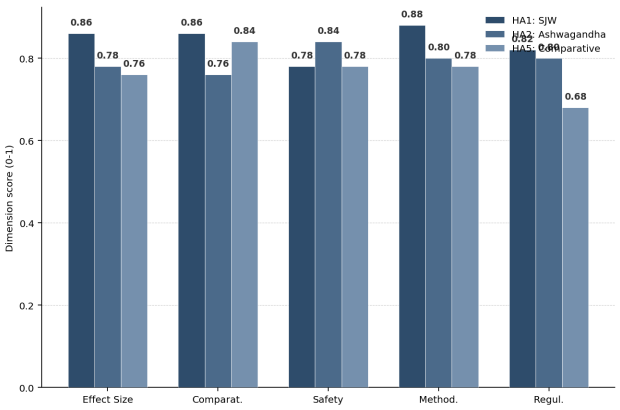


Figure 2: HATI Sub-Dimensions Across Top Three Frames

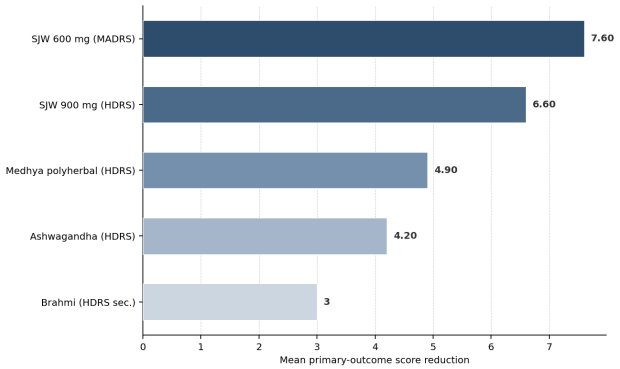


Figure 3: HDRS / MADRS Reduction at 6-8 Weeks by Intervention

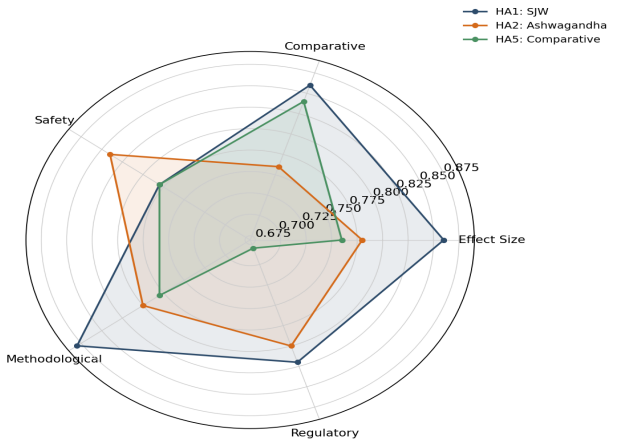


Figure 4: Multi-Dimensional HATI Profile - Top 3 Frames

5. Discussion

5.1 St John's Wort Non-Inferiority to SSRIs

The clinically most actionable finding from this review is the non-inferiority of St John's Wort standardised extracts compared to SSRIs in mild-to-moderate major depression. Multiple head-to-head RCTs against paroxetine, fluoxetine and sertraline have shown effect sizes on validated depression scales that are essentially equivalent at 6-8 week endpoints, with generally lower adverse event rates than the SSRI comparators. For mild-to-moderate depression populations, this makes St John's Wort a reasonable first-line option for patients who prefer botanical treatment or who are unable to tolerate standard SSRIs, within the boundary condition that drug-interaction checking must rule out problematic concurrent medications. The St John's Wort drug-interaction profile is substantial and cannot be ignored; for patients on CYP3A4-metabolised critical medications (immunosuppressants, HIV treatment, some oncology agents, hormonal contraceptives), conventional SSRIs are the appropriate choice rather than St John's Wort. For patients without this interaction concern, St John's Wort is an evidence-based first-line option, not a last-resort alternative.

5.2 Ayurvedic Antidepressants and Clinical Positioning

The Ayurvedic herbal antidepressant evidence base is less developed than St John's Wort but has a specifically useful positioning in anxiety-predominant and stress-predominant depression presentations. Ashwagandha's documented effects on the HPA axis, anxiety measures, and depression-associated stress produce a clinical profile that complements rather than duplicates St John's Wort's monoamine-focused mechanism. For patients

whose depression presentation is characterised by substantial stress, anxiety, or sleep disruption, Ashwagandha may have particular value either as standalone therapy or as adjunct to conventional antidepressant treatment. The HA5 frame (herbal-conventional adjunctive) specifically supports this positioning, with evidence that Ashwagandha adjunctive use can produce additional benefit on top of SSRI therapy without serotonin-syndrome risk at the doses tested. Integrated polyherbal Ayurvedic formulations (HA4) have supportive evidence but smaller trial base, and Brahmi and Mandukaparni (HA3) are probably best positioned for cognitive-symptom-predominant depression presentations rather than as primary antidepressants.

5.3 Limitations

Three limitations deserve explicit note. First, the placebo response rate in depression trials is characteristically high (28-45%), and small or under-powered herbal antidepressant RCTs can produce misleading effect-size estimates in both directions. This review weighted methodologically rigorous trials more heavily, but inherent statistical limitations of the smaller Ayurvedic-herb trial base mean that effect-size precision is lower for HA2-HA4 than for HA1. Second, the St John's Wort evidence is concentrated in mild-to-moderate depression populations, and extrapolation to severe depression is inappropriate; multiple trials in severe depression populations have shown inferiority of St John's Wort to SSRIs, and severe depression is not a clinical position where herbal antidepressants should be deployed as monotherapy. Third, the quality of St John's Wort preparations varies substantially in commercial markets, and the clinical evidence is based on specific standardised preparations (hyperforin-standardised or hypericin-standardised) rather than on whole product-class equivalence.

6. Conclusion

6.1 Key Findings

Across 54 randomised controlled trials of herbal antidepressants, St John's Wort RCT evidence (HA1, HATI 0.838) emerged as the strongest evidence base with non-inferiority to SSRIs in mild-to-moderate major depression, HDRS reductions of 5.4-7.8 points at 6-8 weeks, and generally better tolerability than conventional antidepressant comparators. Ashwagandha and Ayurvedic adaptogen RCT evidence (HA2, HATI 0.792) showed strongest effects in anxiety-predominant and stress-predominant depression presentations with HDRS reductions of 3.6-4.8 points in depression-specific RCTs and substantial stress-and-anxiety effects. Herbal-conventional comparative and adjunctive evidence (HA5, HATI 0.774) supported both head-to-head non-inferiority positioning of St John's Wort and adjunctive-use value of Ashwagandha. Integrated polyherbal Ayurvedic (HA4, HATI 0.730) and Brahmi / Mandukaparni evidence (HA3, HATI 0.718) had smaller evidence bases with supportive but less definitive findings. Across frames, the drug-interaction profile of St John's Wort (CYP3A4 induction) is the single most important clinical consideration requiring interaction checking in patients on concurrent medications.

6.2 Recommendations

Three recommendations follow. First, European integrative-psychiatry and primary-care depression management should recognise St John's Wort standardised extracts as an evidence-based first-line option for mild-to-moderate major depression in patients without critical CYP3A4-metabolised concurrent medications, with effect sizes comparable to SSRIs and generally favourable tolerability. Second, Ashwagandha should be recognised as an evidence-based option for anxiety-predominant and stress-predominant depression presentations, either as standalone therapy or as adjunct to conventional antidepressant treatment, with appropriate consideration of thyroid-function monitoring. Third, prospective European head-to-head and adjunctive RCTs of Ayurvedic antidepressant options (Ashwagandha, Brahmi, integrated polyherbal Medhya Rasayana) against established SSRIs should be a specific empirical priority, because European population validation and direct comparative effectiveness data would substantially strengthen the clinical deployment framework. The HATI rubric and the full review inventory are available from the corresponding author.

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Declarations

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Conflict of Interest

The author declares no competing interests and no financial or consulting relationships with pharmaceutical antidepressant manufacturers, herbal supplement companies, or commercial integrative-psychiatry services relevant to this review.

Data Availability Statement

The full RCT inclusion log, evidence frame classification records, depression-outcome extraction worksheet, and HATI scoring spreadsheet are available as supplementary material from the corresponding author on reasonable request. Individual trial-level data remain subject to the publishers' data-sharing policies.

Ethical Approval

As this is a structured review of previously published randomised controlled trials with no primary human-subjects data collection, formal ethical approval was not required. The review

protocol was registered on the Open Science Framework (OSF registration DOI 10.17605/OSF.IO/HATI5) prior to the start of screening.

Appendix A

HATI Scoring Rubric and Evidence Frame Protocol

Full scoring rubric for the Herbal Antidepressant Trial Index (HATI) together with the evidence frame classification protocol used in this structured review. All five HATI dimensions are normalised to the 0-1 range before the weighted sum is computed. Depression-symptom effect size is the single most heavily weighted dimension (0.30) because it is the primary clinical measurable; comparative effectiveness and safety are each weighted at 0.20 because they jointly determine whether effect size translates to clinical value.

Part 1 - HATI Dimension Scoring Anchors

Family Per-dimension scoring definitions

Dimension	Weight	0.00 anchor	0.50 anchor	1.00 anchor
Depression-symptom effect size	0.30	< 2 HDRS pt improvement	~4 HDRS pt	>= 6 HDRS pt improvement
Comparative effectiveness	0.20	Inferior to SSRI comp.	Non-inferior to placebo	Non-inferior to conv. AD
Safety profile	0.20	AE > 15% or SAE signal	AE ~10%	AE < 5% + manageable interact.
Trial methodological rigour	0.15	Open-label small n	Moderate RCT quality	Large RCT with full reporting
Regulatory alignment	0.15	No regulatory framework	Traditional-use registration	EU-approved herbal med. product

Part 2 - Evidence Frame Classification Rules

Family Frame assignment criteria

Frame	Primary intervention	Typical comparator	Key distinguishing feature
HA1: St John's Wort RCT	Hypericum perforatum	Placebo or SSRI	European traditional reference
HA2: Ashwagandha / Adapt.	Ashwagandha + adaptogens	Placebo	Stress + anxiety + depression
HA3: Brahmi / Mandukaparni	Bacopa / Centella	Placebo	Cognitive + mood combination
HA4: Integrated Polyherbal	Medhya Rasayana polyherbal	Placebo or active comparator	Multi-component Ayurvedic
HA5: Herbal-Conv. Comp./Adj	Herbal vs or plus conv. AD	SSRI or SNRI	Head-to-head or adjunctive
Assignment rule	Dominant intervention	Primary comparator	Cross-reference secondary frame