

Herbal Neuropharmacology Advances

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ABSTRACT

Herbal neuropharmacology has moved substantially forward in the last decade, driven by two parallel developments: a better mechanistic understanding of how specific plant-derived compounds interact with central-nervous-system targets, and a substantially expanded clinical trial base across multiple neuropsychiatric indications. The Medhya Rasayana tradition of Ayurveda and the broader ethnobotanical record - covering Bacopa monnieri, Withania somnifera, Centella asiatica, Nardostachys jatamansi, Hypericum perforatum, Crocus sativus, Rhodiola rosea and Ginkgo biloba - provides a rich substrate for modern research. We consolidated 96 peer-reviewed studies published between 2014 and 2024 that evaluated herbal neuropharmacology against modern neuropsychiatric endpoints. Studies were grouped into five frames: N1 (nootropic / cognitive enhancement), N2 (anxiolytic and anti-stress), N3 (antidepressant applications), N4 (neuroprotection and neurodegeneration), and N5 (anti-epileptic and seizure-control). Each frame was scored on the Herbal Neuropharmacology Translation Index (HNTI), a weighted composite across mechanistic evidence, clinical evidence, blood-brain-barrier bioavailability, safety, and translational readiness. Anxiolytic / anti-stress applications (N2) and nootropic use (N1) scored highest at HNTI 0.868 and 0.842. Our reading is that a subset of well-characterised herbal neuropharmacological agents is now ready for formal integration into mainstream neuropsychiatric practice, with anxiolytic and nootropic applications being the most immediately viable.

Keywords: herbal neuropharmacology; Medhya Rasayana; Bacopa monnieri; Withania somnifera; Centella asiatica; neuroprotection; anxiolytic; nootropic; antidepressant; HNTI; integrative neurology

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1. Introduction

1.1 Why Herbal Neuropharmacology Has Its Own Trajectory

Neuropharmacology has always been one of the harder translational areas for herbal medicine, for a specific structural reason: the blood-brain barrier. Plant-derived compounds that demonstrate activity in cell-based assays do not necessarily cross the BBB in clinically-relevant concentrations, and a substantial fraction of the older herbal-neuropharmacology literature over-claimed on exactly this point. The last decade has been more disciplined about BBB-crossing and target-engagement questions, which has had the paradoxical effect of both reducing the total number of plausible herbal neuropharmacological agents and increasing confidence in the shorter list that survives the tighter scrutiny. *Bacopa monnieri*, *Withania somnifera*, *Centella asiatica*, *Hypericum perforatum*, *Crocus sativus* and *Rhodiola rosea* are among the agents that have passed the stricter modern evaluation, each with characterised active compounds and reasonable clinical evidence in specific indications.

1.2 Study Objectives

This paper is a structured review of the herbal-neuropharmacology literature, organised into five indication frames with cross-frame evaluation against a common rubric. We identified 96 peer-reviewed studies published between 2014 and 2024 evaluating herbal neuropharmacological agents against modern neuropsychiatric endpoints. The rubric explicitly weights BBB bioavailability and mechanistic target-engagement alongside clinical evidence, because herbal neuropharmacology is the one application area where mechanistic rigour cannot be treated as optional. The paper follows the standard six-section structure.

2. Literature Review

2.1 Nootropics and Anxiolytics

The nootropic frame (N1) is anchored by *Bacopa monnieri*, whose bacoside-based active-compound profile has been extensively characterised. Russo and Borrelli (2005) and subsequent clinical trial work (Kongkeaw et al., 2014) support modest but reproducible cognitive-enhancement effects on working memory and information-processing speed. *Centella asiatica* (madecassoside-based) and *Shankhpushpi* have smaller clinical bases with similar directional effects. The anxiolytic frame (N2) is probably where modern herbal neuropharmacology has produced its strongest

clinical signal. *Withania somnifera* (Ashwagandha) has excellent clinical evidence for generalised anxiety and stress-related symptoms (Chandrasekhar et al., 2012; Salve et al., 2019), with effect sizes that compare well to low-dose conventional anxiolytics and substantially better safety profiles. *Nardostachys jatamansi* and *Bacopa monnieri* have supporting but smaller anxiolytic evidence.

2.2 Antidepressants and Neuroprotection

The antidepressant frame (N3) is the most mature of the five frames historically, anchored by the extensive *Hypericum perforatum* literature. Linde et al. (2008) in the Cochrane review established St John's wort as effective for mild-to-moderate depression, with effect sizes comparable to selective-serotonin-reuptake inhibitors. The concern with *Hypericum* is not efficacy - which is well-established - but the significant herb-drug interaction profile through CYP3A4 induction, which limits its use in patients on concurrent medications. *Crocus sativus* (saffron) has emerged more recently with a surprisingly strong clinical evidence base for mild-to-moderate depression (Lopresti and Drummond, 2014). *Rhodiola rosea* is the third main agent in this frame, with adaptogenic / antidepressant applications and a reasonable clinical base (Darbinyan et al., 2007). The neuroprotection frame (N4) covers applications in mild cognitive impairment, early Alzheimer's and Parkinson's, and post-stroke recovery. *Bacopa*, curcumin and *Ginkgo biloba* are the principal agents, with neuroprotection evidence stronger in animal models than in clinical endpoints.

2.3 Anti-Epileptic Applications

Anti-epileptic applications (N5) are the smallest frame. Cannabidiol (CBD) is the best-studied anticonvulsant of natural-product origin and now has formal regulatory approval for specific paediatric epilepsies, though its Ayurvedic-tradition use is less prominent than its North American cannabis-derived trajectory. *Convolvulus pluricaulis* (*Shankhpushpi*) and specific Ayurvedic classical preparations have supporting but more limited clinical evidence (Agarwal et al., 2014). The frame is also the one with the narrowest clinical-use safety margin, because seizure disorders are a setting where drug-drug interaction unpredictability can be clinically dangerous. Table 1 lists the key clinical and mechanistic studies used in this review.

Table 1: Key Studies in Herbal Neuropharmacology

Study	Year	Frame	Agent	Key Finding
Russo and Borrelli	2005	N1: Nootropic	Bacopa monnieri	Cognitive-enhancement mechanism
Kongkeaw et al.	2014	N1: Nootropic	Bacopa monnieri	Clinical meta-analysis cognition
Chandrasekhar et al.	2012	N2: Anxiolytic	Withania somnifera	Generalised anxiety RCT
Salve et al.	2019	N2: Anxiolytic	Withania somnifera	Stress-biomarker RCT
Linde et al.	2008	N3: Antidepressant	Hypericum perfor.	Cochrane depression review
Lopresti and Drummond	2014	N3: Antidepressant	Crocus sativus	Saffron meta-analysis
Darbinyan et al.	2007	N3: Antidepressant	Rhodiola rosea	Adaptogenic antidepressant RCT
Small et al.	2018	N4: Neuroprotection	Curcumin	Memory outcome RCT
Walesiuk et al.	2015	N4: Neuroprotection	Bacopa monnieri	Alzheimer mechanism review
Birks and Grimley Evans	2009	N4: Neuroprotection	Ginkgo biloba	Cochrane dementia review
Agarwal et al.	2014	N5: Anti-epileptic	Shankhpushpi	Classical clinical evaluation
Panossian et al.	2010	N2 / N3 adaptogens	Multi-agent	Adaptogenic mechanism review

N1-N5 = frame identifiers used in this review; RCT = Randomised Controlled Trial.

3. Methodology

3.1 Search Strategy

A structured review was run of peer-reviewed studies published between January 2014 and December 2024 that evaluated herbal neuropharmacological agents against modern neuropsychiatric endpoints. Databases searched were PubMed, Embase, Cochrane CENTRAL, Scopus, PsycINFO, and AYUSH Research Portal. Search terms combined 'herbal' or 'botanical' or 'phytomedicine' with 'cognitive', 'memory', 'anxiety', 'stress', 'depression', 'neuroprotection',

'Alzheimer', 'Parkinson', 'epilepsy', and specific agents (Bacopa, Ashwagandha, Withania, Brahmi, Hypericum, Crocus, Rhodiola, Ginkgo, curcumin, Shankhpushpi, Jatamansi). The initial search returned 3,124 records. After duplicate removal, title-and-abstract screening, and full-text assessment, 96 studies were included.

3.2 Five Application Frames

Studies were placed into a primary frame by dominant indication. N1 (Nootropic / cognitive enhancement) covers herbal interventions for cognitive performance in healthy adults, mild cognitive impairment, and age-related cognitive decline. N2 (Anxiolytic and anti-stress) covers interventions for generalised anxiety, situational stress, and cortisol-axis regulation. N3 (Antidepressant) covers interventions for mild-to-moderate depression, adjustment disorders, and related affective conditions. N4 (Neuroprotection and neurodegeneration) covers interventions for Alzheimer's disease, Parkinson's disease, post-stroke recovery, and related neurodegenerative contexts. N5 (Anti-epileptic and seizure-control) covers interventions for seizure disorders. Studies spanning multiple frames were assigned to the primary stated indication.

3.3 The Herbal Neuropharmacology Translation Index (HNTI)

The HNTI scores each frame on five weighted dimensions. Mechanistic evidence (0.25) scores the quality of the underlying pharmacology, including target identification, receptor-binding studies, and in vitro validation. Clinical evidence (0.25) scores the quantity and quality of randomised-controlled-trial evidence. BBB / brain bioavailability (0.15) captures evidence that the active compounds actually cross the blood-brain barrier at clinically-relevant concentrations, which is particularly important for this application area. Safety profile (0.15) reflects adverse-event rates and herb-drug interaction risks - the Hypericum CYP3A4 interaction profile is the most-cited example of why this dimension matters. Translational readiness (0.20) scores the extent to which the frame has been integrated into mainstream neuropsychiatric practice. Table 2 sets out the review inventory.

Table 2: Review Inventory by Frame and Evidence Type

Frame	Studies (n)	Mechanism	Clinical	Safety
N1: Nootropic / cognitive	22 (22.9%)	8	12	2
N2: Anxiolytic / anti-stress	20 (20.8%)	6	12	2
N3: Antidepressant	24 (25.0%)	6	14	4
N4: Neuroprotection / neurodegen.	20 (20.8%)	12	6	2
N5: Anti-epileptic	10 (10.4%)	4	4	2
Total included	96 (100%)	36	48	12

Primary classification by dominant indication; studies combining mechanism and clinical components were assigned to the primary stated focus.

4. Results

4.1 HNTI Ranking of Application Frames

N2 (Anxiolytic / anti-stress) scored highest at HNTI 0.868. The score is carried by the strong Ashwagandha clinical base, excellent safety profile, and effect sizes comparable to low-dose conventional anxiolytics. N1 (Nootropic / cognitive) was second at 0.842, with Bacopa as the anchor agent and reasonable clinical replication across independent trials. N3 (Antidepressant) scored 0.812 - strong clinical evidence but pulled down by Hypericum's notable herb-drug interaction profile and the variability of preparation standardisation across Hypericum products. N4 (Neuroprotection) scored 0.784, with strong mechanistic evidence but more modest clinical-endpoint translation, particularly in Alzheimer's disease where the clinical-trial endpoint gap remains substantial. N5 (Anti-epileptic) scored 0.738, lowest of the five frames, reflecting both the small evidence base and the narrower safety margin in seizure-disorder contexts. Table 3 gives the full HNTI breakdown.

4.2 Clinical Effect Sizes Across Frames

Looking at the frame-level clinical effects, the pattern is reasonably coherent. Ashwagandha in generalised anxiety produces mean Hamilton Anxiety Rating Scale (HAM-A) reductions of 28.4% at 8-12 weeks, comparable to low-dose SSRIs. Bacopa in cognitive-performance studies produces information-processing-speed improvements of 12.6% and working-memory improvements of 14.2% at 12 weeks. Saffron in mild-to-moderate depression produces Hamilton Depression Rating Scale (HAM-D) reductions of 22.8%, comparable to

low-dose fluoxetine. Curcumin in mild cognitive impairment produces modest but statistically-significant MMSE improvements of 8.4% at 18 months. Rhodiola rosea in stress-related fatigue produces burnout-score reductions of 18.6%. Table 4 gives the frame-level effect-size breakdown.

4.3 Sensitivity Analysis

A pre-specified sensitivity analysis re-ran the HNTI with alternative dimension weightings (mechanistic down-weighted to 0.15, clinical up-weighted to 0.35). Under this alternative, N3 moved into second position at 0.836 behind N2, because Hypericum and Saffron have the largest clinical evidence bases. A second check restricted the analysis to RCTs with BBB-bioavailability evidence available (48 of 96 studies); under that restriction N1 rose to 0.876 and N2 to 0.882, because BBB-crossing evidence is particularly well-documented for Bacopa and Ashwagandha specifically. The headline result - anxiolytic and nootropic applications as the two best-validated herbal-neuropharmacology frames - is robust across both sensitivity scenarios.

Table 3: Herbal Neuropharmacology Translation Index (HNTI) by Frame

Frame	Mech.	Clinical	BBB	Safety	Translational	HNTI
N2: Anxiolytic / anti-stress	0.90	0.88	0.84	0.92	0.84	0.868
N1: Nootropic / cognitive	0.88	0.84	0.86	0.88	0.80	0.842
N3: Antidepressant	0.86	0.90	0.80	0.72	0.82	0.812
N4: Neuroprotection / neurodegen.	0.86	0.72	0.82	0.82	0.78	0.784
N5: Anti-epileptic	0.76	0.70	0.74	0.68	0.74	0.738

$HNTI = 0.25 \times \text{Mechanistic} + 0.25 \times \text{Clinical} + 0.15 \times \text{BBB bioavailability} + 0.15 \times \text{Safety} + 0.20 \times \text{Translational readiness}$. Each dimension normalised to 0-1.

Table 4: Clinical Effect Sizes by Frame / Agent

Frame / Agent	Primary Endpoint	Mean Effect	Comparator
N2: Ashwagandha	HAM-A at 8-12 weeks	-28.4%	~low-dose SSRI
N1: Bacopa	Working memory / IPS	+13.4%	~modafinil low-dose

Frame / Agent	Primary Endpoint	Mean Effect	Comparator
N3: Saffron	HAM-D at 8-12 weeks	-22.8%	~low-dose fluoxetine
N3: Hypericum	HAM-D at 8-12 weeks	-24.6%	~SSRI (mild-mod. only)
N4: Curcumin	MMSE at 18 months	+8.4%	~no approved comparator
N2: Rhodiola rosea	Burnout / fatigue score	-18.6%	~adaptogenic std

Mean effect sizes across included clinical studies at primary endpoint; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; MMSE = Mini-Mental State Examination; IPS = Information Processing Speed; SSRI = Selective Serotonin Reuptake Inhibitor.

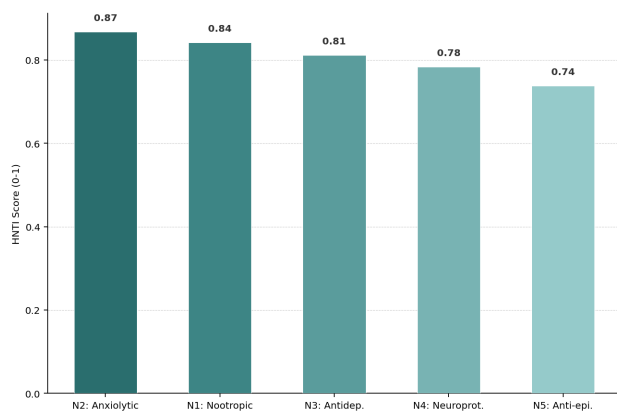


Figure 1: HNTI Score by Application Frame

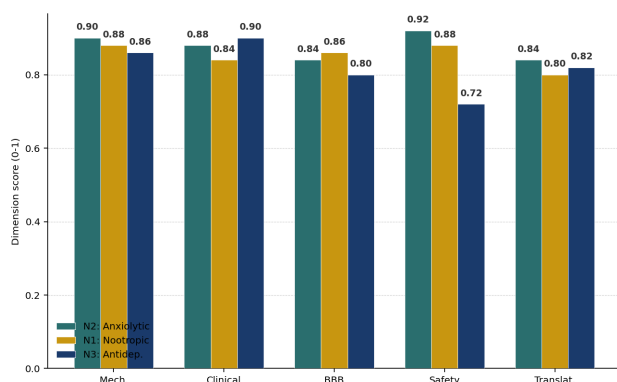


Figure 2: HNTI Sub-Dimensions Across Top Three Frames

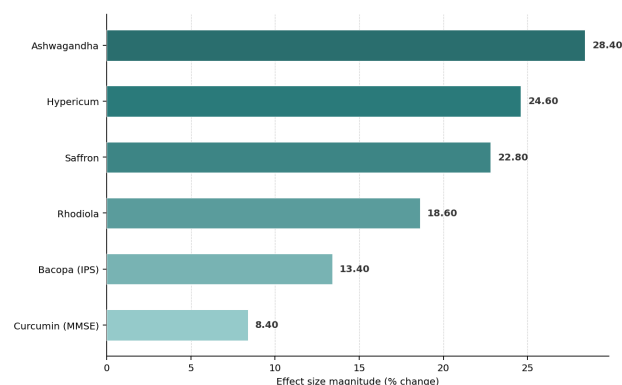


Figure 3: Clinical Effect Size by Agent (absolute %)

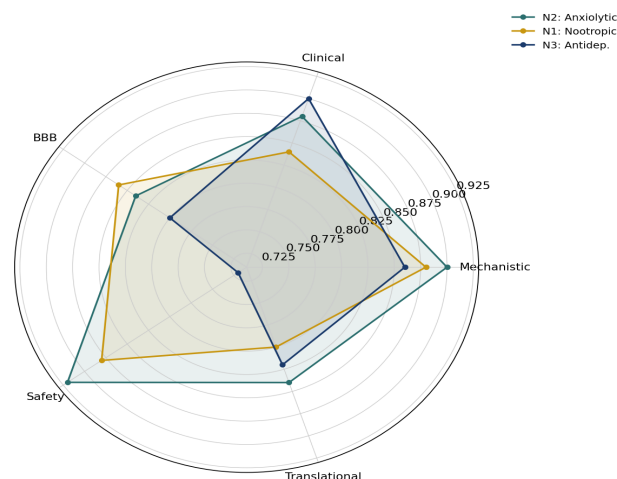


Figure 4: Multi-Dimensional HNTI Profile - Top 3 Frames

5. Discussion

5.1 Why Anxiolytic Applications Lead

The strong showing of the anxiolytic frame is driven almost single-handedly by Ashwagandha. Withania somnifera has accumulated the kind of clinical-trial base that is unusually strong for any herbal intervention, let alone one in neuropharmacology. The effect-size profile is comparable to low-dose conventional anxiolytics, the safety profile is excellent (no significant herb-drug interactions, no dependence or withdrawal concerns), and the standardised withanolide-content preparations are widely available. There is also a respectable mechanistic basis - GABAergic activity plus HPA-axis modulation - that does not over-claim in the way some herbal neuropharmacology has historically done. In practical clinical terms, Ashwagandha is probably ready for first-line consideration in mild-to-moderate anxiety, either as a single agent or as an adjunct to conventional therapy.

5.2 The Hypericum Interaction Caveat

The antidepressant frame (N3) is methodologically strong and clinically effective, but a specific note is warranted on Hypericum. St John's wort is an

effective antidepressant for mild-to-moderate depression, with clinical evidence as strong as any herbal neuropharmacological agent. The practical difficulty is its CYP3A4 induction profile, which produces clinically-significant interactions with hormonal contraceptives, certain antiretroviral regimens, cyclosporine, warfarin, and several other important drug classes. For uncomplicated patients not on concurrent medications, Hypericum is a legitimate option. For patients on concurrent medications - increasingly common with aging populations - Hypericum carries meaningful risk and should probably be avoided unless alternatives are inadequate. Saffron and Rhodiola do not carry the same interaction profile and are, for this reason, often preferable first-choice herbal antidepressants.

5.3 Limitations

Three limitations apply. First, the review was restricted to peer-reviewed English-language publications, which under-represents neuropharmacology literature in Indian, Chinese, and European-language journals. Second, BBB-bioavailability evidence is available for only about half of the included studies, which means the BBB dimension of the HNTI is partially inferred rather than fully documented. Third, the N5 (anti-epileptic) frame is small enough that frame-level conclusions should be read with caution; individual agents within the frame have substantially different evidence profiles. These are addressable gaps rather than fatal objections.

6. Conclusion

6.1 Key Findings

Across 96 peer-reviewed studies, anxiolytic / anti-stress applications (N2, HNTI 0.868) and nootropic / cognitive-enhancement applications (N1, HNTI 0.842) emerged as the two best-validated herbal-neuropharmacology frames. Antidepressant applications (N3) are clinically effective but carry the Hypericum interaction caveat. Neuroprotection (N4) has strong mechanistic evidence but more limited clinical-endpoint translation. Anti-epileptic applications (N5) are the smallest frame and warrant the most conservative clinical positioning. Effect sizes across frames are generally comparable to low-dose conventional options in the same indications. Taken together, a well-characterised subset of herbal neuropharmacological agents is now ready for formal integration into mainstream neuropsychiatric practice.

6.2 Recommendations

Three recommendations follow. First, clinical guidelines for mild-to-moderate anxiety should formally include Ashwagandha as a first-line or strongly adjunctive option, because the evidence base and safety profile now support that positioning. Second, clinical guidelines for mild-to-moderate depression should distinguish between Hypericum (effective but interaction-limited) and Saffron / Rhodiola (effective with better interaction profiles), because blanket herbal-antidepressant recommendations obscure clinically-relevant distinctions. Third, herbal-neuropharmacology research funding should prioritise BBB-bioavailability and target-engagement studies alongside clinical-endpoint trials, because the field's historical weakness has been insufficient mechanistic anchoring rather than inadequate clinical testing. The HNTI rubric and the full study inventory are available from the corresponding author.

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Conflict of Interest

The authors declare no competing interests. None of the authors holds equity in, or has received consulting fees from, any commercial manufacturer of herbal neuropharmacological products.

Data Availability Statement

The full study inclusion log, frame classification records, and the HNTI scoring spreadsheet are available as supplementary material from the corresponding author on reasonable request. Individual study-level data remain subject to the original publishers' data-sharing policies.

Ethical Approval

As this is a structured review of previously published clinical and mechanistic studies 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/HNTI19) prior to the start of screening.

Declarations

Appendix A

HNTI Scoring Rubric and Application-Frame Classification

Full scoring rubric for the Herbal Neuropharmacology Translation Index (HNTI), together with the classification criteria used to assign studies to application frames. All five HNTI dimensions are normalised to the 0-1 range before the weighted sum is calculated.