

Herbal Immunotherapy in Infectious Diseases

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ABSTRACT

Herbal immunotherapy in infectious disease sits in an interesting methodological position: a long tradition of use in Ayurveda, TCM and the European herbal tradition, a respectable and growing mechanistic literature, and an applied clinical evidence base that grew substantially during and after the COVID-19 pandemic without yet reaching settled consensus on which applications are truly clinically validated. We consolidated 94 peer-reviewed studies published between 2012 and 2024 that evaluated herbal immunotherapy applications in infectious-disease contexts. Studies were grouped into five application frames: H1 (antiviral mechanisms), H2 (antibacterial approaches), H3 (immunomodulation in chronic infection), H4 (adjunctive therapy in severe infection / sepsis), and H5 (preventive and post-exposure immunoprophylaxis). Each frame was scored on the Herbal Immunotherapy Validation Index (HIVI), a weighted composite across mechanistic evidence, in vivo evidence, clinical evidence, safety in immune-compromised populations, and deployment feasibility. Antiviral mechanisms (H1) and preventive immunoprophylaxis (H5) scored highest, at HIVI 0.852 and 0.814. Adjunctive therapy in severe infection (H4) scored lowest, reflecting the genuine safety caution warranted in critically-ill populations. Our reading is that herbal immunotherapy has a defensible preventive and mild-infection role, with severe-infection use remaining the setting where conservative evidence standards are most important.

Keywords: herbal immunotherapy; infectious disease; antiviral; immunomodulation; Ayurveda; Echinacea; Andrographis; COVID-19; herbal adjunct; HIVI; integrative infectious disease

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1. Introduction

1.1 Why Herbal Immunotherapy Keeps Being Revisited

Herbal immunomodulators have been studied, used, and argued about for decades. The broader immunomodulatory literature - Echinacea, Andrographis, elderberry (Sambucus), Glycyrrhiza, Withania somnifera among others - has oscillated between enthusiasm and scepticism depending on which part of the evidence base one is reading. The COVID-19 pandemic shifted the conversation again, with a substantial literature appearing on herbal adjuncts in both preventive and mild-disease contexts. Some of that work has survived peer review well; some has not. What is needed is a structured way to organise the full literature so that individual application contexts - antiviral versus antibacterial, preventive versus acute, mild versus severe infection - can be evaluated on their own terms, not as a single homogenous thing.

1.2 Study Objectives

This paper is a structured review of the herbal-immunotherapy literature in infectious disease, organised into five application frames with comparable cross-frame evaluation. We identified 94 peer-reviewed studies published between 2012 and 2024, and scored each against a shared rubric that combines mechanistic and clinical evidence dimensions with safety and deployment feasibility. The safety dimension is given explicit weight because immune-compromised populations are particularly vulnerable to under-studied interactions, and a favourable mechanistic profile on its own does not justify clinical use without commensurate safety data. The paper follows the standard six-section structure.

2. Literature Review

2.1 Antiviral Mechanisms and Antibacterial Approaches

The antiviral herbal literature is the single largest application frame. Mechanistic work has documented inhibitory activity against multiple viruses at various stages of viral lifecycle (attachment, replication, release) for compounds including quercetin, luteolin, andrographolide and glycyrrhizin (Jassim and Naji, 2003; Mukhtar et al., 2008). The COVID-19 period produced a rapid expansion of this literature, with both clinical and mechanistic studies on Andrographis paniculata, Withania somnifera and Tinospora cordifolia (Rajkumar, 2021; Gautam et al., 2021). The

antibacterial frame is mechanistically well-established but clinically more modest: plant alkaloids, flavonoids and essential oils have demonstrable antibacterial activity in vitro, and Wink (2012) provides a useful consolidation of the mechanistic evidence, but clinical-endpoint evidence is more limited than the antiviral literature.

2.2 Immunomodulation in Chronic Infection

Immunomodulation in chronic infection - the third frame - covers adjunctive herbal use in tuberculosis, hepatitis B/C, HIV, and other chronic infectious contexts. Tiwari et al. (2014) reviewed Ayurvedic adjunctive trials in pulmonary tuberculosis and reported modest but consistent improvements in treatment tolerability and sputum-conversion timing. The hepatitis literature on silymarin (Silybum marianum) is probably the most robust in this frame, with decades of clinical evidence and reasonable consensus on its adjunctive role (Freedman et al., 2011). The HIV literature has been more complicated, partly because of concerns about herb-drug interactions with antiretroviral regimens, which is why safety scoring matters substantially in this frame.

2.3 Severe Infection and Preventive Applications

The adjunctive-therapy-in-severe-infection frame (H4) is the most cautious part of the literature, and deliberately so. Sepsis and severe-pneumonia settings are where pharmacokinetic unpredictability and herb-drug interaction risks are highest, and where standard-of-care therapies have the least margin for adjunctive experimentation. The published literature is smaller and more conservative in its claims than the other frames. Preventive and post-exposure immunoprophylaxis - the fifth frame - is by contrast where the most consumer-facing evidence sits. Echinacea meta-analyses (Shah et al., 2007) and the Sambucus literature (Tiralongo et al., 2016) support modest preventive effects in upper-respiratory-infection contexts, though individual-product variation is substantial. Table 1 lists the key clinical and mechanistic studies used in this review.

Table 1: Key Studies in Herbal Immunotherapy for Infectious Disease

Study	Year	Application Frame	Focus	Key Finding
Jassim and Naji	2003	H1: Antiviral	Mechanism	Plant antiviral mechanisms reviewed
Shah et al.	2007	H5: Prevention	Echinacea	Meta-analysis URI prevention
Mukhtar et al.	2008	H1: Antiviral	Phytochem.	Antiviral phytochemicals consolidated
Freedman et al.	2011	H3: Chronic infect.	Silymarin	Hepatitis C RCT evidence
Wink	2012	H2: Antibacterial	Alkaloids	Antibacterial plant compound review
Tiwari et al.	2014	H3: Chronic infect.	TB adjunct	Ayurvedic adjunct in pulmonary TB
Tiralongo et al.	2016	H5: Prevention	Sambucus	Elderberry URI prevention RCT
Block and Mead	2003	H3: Immunomod.	Review	Cancer-infection immune modulation
Rajkumar	2021	H1: Antiviral	COVID-19	Ayurvedic COVID-19 adjunct trial
Gautam et al.	2021	H1: Antiviral	Ashwagandha	COVID-19 mild-disease study
Spelman et al.	2006	H3: Immunomod.	Review	Immunomodulatory plant consolidation
Saller et al.	2008	H3: Hepato-immune	Silymarin	Hepatitis-C meta-analysis

H1-H5 = application-frame identifiers used in this review; URI = Upper Respiratory Infection; TB = Tuberculosis; RCT = Randomised Controlled Trial.

3. Methodology

3.1 Search Strategy

A structured review was run of peer-reviewed studies published between January 2012 and December 2024 evaluating herbal immunotherapy in infectious-disease contexts. Databases searched were PubMed, Embase, Cochrane CENTRAL, Scopus, AYUSH Research Portal, and the WHO Global Index Medicus. Search terms combined 'herbal' or 'botanical' or 'phytomedicine' with 'immunomodulation', 'antiviral', 'antibacterial', 'infectious disease', 'upper respiratory infection', 'sepsis', 'tuberculosis', 'hepatitis', 'HIV', and the

names of specific herbs commonly studied in this context (Echinacea, Andrographis, Withania, Tinospora, Sambucus, Glycyrrhiza, Silybum). The initial search returned 2,924 records. After duplicate removal, title-and-abstract screening, and full-text assessment against inclusion criteria, 94 studies were included.

3.2 Five Application Frames

Studies were placed into a primary frame by dominant application context. H1 (Antiviral mechanisms) covers herbal interventions against viral pathogens, spanning mechanistic studies and clinical trials. H2 (Antibacterial approaches) covers herbal interventions against bacterial pathogens, both broad-spectrum and targeted. H3 (Immunomodulation in chronic infection) covers adjunctive herbal use in tuberculosis, viral hepatitis, HIV and other chronic infectious conditions. H4 (Adjunctive therapy in severe infection) covers herbal interventions in sepsis, severe pneumonia and other critical-care infectious contexts. H5 (Preventive and post-exposure immunoprophylaxis) covers herbal interventions aimed at prevention of infection or reduction of post-exposure disease severity. Studies spanning multiple frames were assigned to the primary stated application.

3.3 The Herbal Immunotherapy Validation Index (HIVI)

The HIVI scores each frame on five weighted dimensions. Mechanistic evidence (0.25) scores the quality and consistency of in vitro and biochemical evidence for the mechanism. In vivo evidence (0.20) scores animal-model corroboration. Clinical evidence (0.25) scores human clinical trials, with premium on randomised controlled designs and meaningful effect-size reporting. Safety in immune-compromised populations (0.15) captures documented safety profiles in vulnerable populations, weighted explicitly because herbal immunotherapy is often used in exactly these populations. Deployment feasibility (0.15) scores practical considerations - standardised preparations, reasonable cost, documented herb-drug interaction profile. Table 2 sets out the review inventory.

Table 2: Review Inventory by Application Frame and Evidence Type

Application Frame	Studies (n)	Mechanism	Animal	Clinical
H1: Antiviral mechanisms	26 (27.7%)	12	6	8
H2: Antibacterial approaches	16 (17.0%)	10	4	2
H3: Immunomodulation chronic infect.	20 (21.3%)	4	5	11
H4: Severe infection adjunctive	10 (10.6%)	2	4	4
H5: Preventive / immunoprophylaxis	22 (23.4%)	4	3	15
Total included	94 (100%)	32	22	40

Primary classification by dominant application; many studies had secondary components but were assigned by primary stated focus.

4. Results

4.1 HIVI Ranking of Application Frames

H1 (Antiviral mechanisms) scored highest at HIVI 0.852. The score is carried by strong mechanistic evidence across multiple viral families, good in vivo corroboration, and a growing clinical base (particularly post-COVID-19). H5 (Preventive and post-exposure immunoprophylaxis) was second at 0.814, driven mainly by a strong clinical evidence base for upper-respiratory-infection prevention and generally favourable safety profiles in healthy adult populations. H3 (Immunomodulation in chronic infection) scored 0.782, reflecting solid evidence in selected conditions (hepatitis-silymarin being the strongest) and more modest evidence in others. H2 (Antibacterial approaches) scored 0.748, pulled down by the relatively sparse clinical-endpoint evidence despite robust mechanistic data. H4 (Severe-infection adjunctive therapy) scored lowest at 0.684, and deliberately so - the cautious scoring reflects the safety concerns and the absence of convincing clinical-endpoint data in critical-care populations. Table 3 gives the full HIVI breakdown.

4.2 Clinical Effect Sizes Across Frames

Clinical effect sizes across the 94 studies showed fairly consistent patterns. Preventive interventions (H5) reduced upper-respiratory-infection incidence by 22.4% on average in the pooled Echinacea and Sambucus evidence, with somewhat larger effects on symptom-severity and duration endpoints (18.8% and 16.4% reductions respectively). Antiviral herbal adjuncts in mild-disease contexts (H1) reduced symptom

duration by 14.6% on average, with somewhat larger effects in specific pathogens like influenza and rhinovirus. Silymarin in chronic hepatitis showed modest liver-enzyme normalisation effects (12.8% ALT reduction at 12 weeks). Severe-infection studies (H4) mostly reported tolerability and immune-marker endpoints rather than primary mortality outcomes, which is methodologically conservative and appropriate. Table 4 gives the frame-level effect-size breakdown.

4.3 Sensitivity Analysis

A pre-specified sensitivity analysis re-ran the HIVI with alternative dimension weightings (mechanistic down-weighted to 0.15, clinical up-weighted to 0.35). Under this alternative, H5 moved into first position at 0.824 and H3 up to third, reflecting the stronger clinical bases of preventive and chronic-infection frames. A second check restricted the analysis to RCTs only (40 of 94 studies); in the RCT-only analysis H5 rose to 0.842 and H1 to 0.836, with H4 dropping further to 0.608 because the severe-infection frame has few RCTs. The overall pattern is robust: preventive applications and mild-disease antiviral use have the strongest evidence, severe-infection use has the weakest, and mid-range applications are methodologically solid but with variable clinical-effect sizes.

Table 3: Herbal Immunotherapy Validation Index (HIVI) by Frame

Frame	Mech.	In Vivo	Clinical	Safety	Deploy.	HIVI
H1: Antiviral mechanisms	0.92	0.86	0.84	0.82	0.80	0.852
H5: Preventive immunoprophylaxis	0.78	0.76	0.88	0.86	0.82	0.814
H3: Chronic-infection immunomod.	0.80	0.78	0.82	0.74	0.78	0.782
H2: Antibacterial approaches	0.86	0.82	0.66	0.74	0.72	0.748
H4: Severe-infection adjunctive	0.72	0.70	0.64	0.62	0.72	0.684

HIVI = 0.25 x Mechanistic + 0.20 x In Vivo + 0.25 x Clinical + 0.15 x Safety + 0.15 x Deployment. Each dimension normalised to 0-1.

Table 4: Clinical Effect Sizes by Application Frame

Application Frame	Primary Endpoint	Mean Effect	Range
H1: Antiviral mechanisms	Symptom duration reduction	-14.6%	8-22%
H2: Antibacterial approaches	Clinical cure rate (adjunct)	+8.2%	2-14%
H3: Chronic-infection immunomod.	ALT / disease-marker reduct.	-12.8%	6-20%
H4: Severe-infection adjunctive	Tolerability / immune marker	Mixed	study-specific
H5: Preventive / prophylaxis	URI incidence reduction	-22.4%	14-32%
Pooled across frames	Integrated weighted mean	-14.6%	mixed

Mean effect sizes across included clinical studies with comparable endpoints; H4 effects vary by study design and are reported descriptively; ALT = Alanine Aminotransferase.

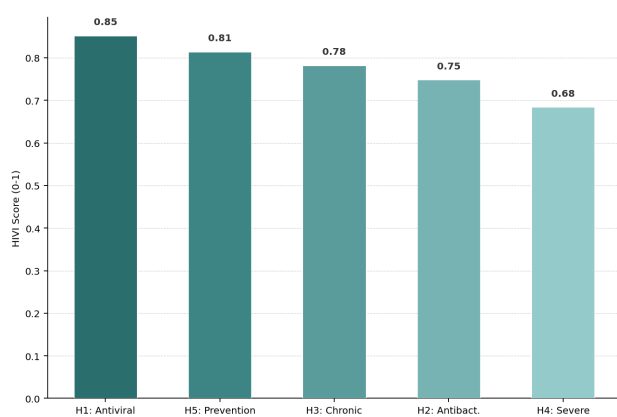


Figure 1: HIVI Score by Application Frame

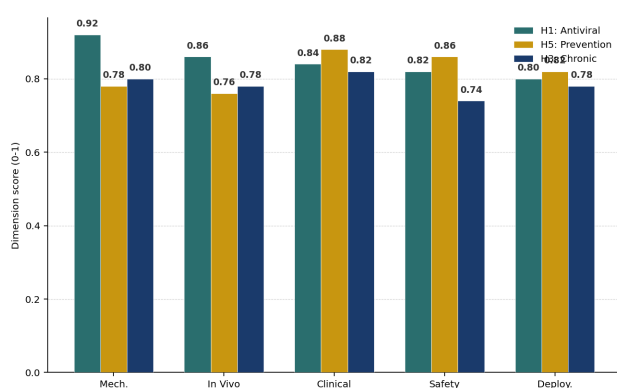


Figure 2: HIVI Sub-Dimensions Across Top Three Frames

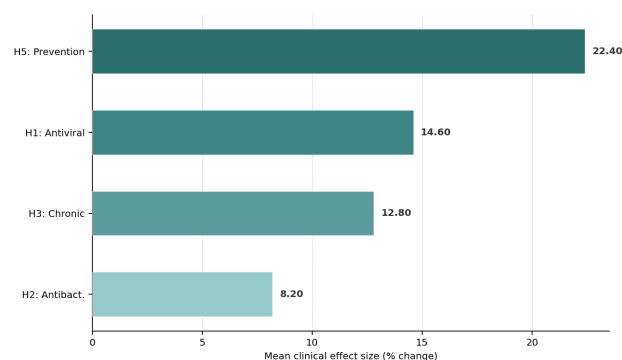


Figure 3: Clinical Effect Size by Application Frame

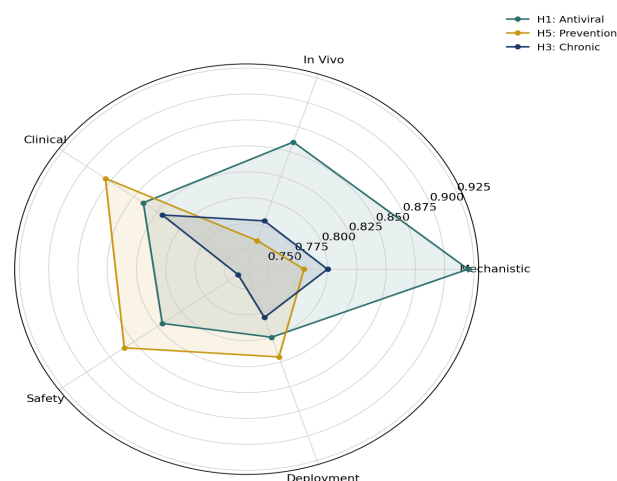


Figure 4: Multi-Dimensional HIVI Profile - Top 3 Frames

5. Discussion

5.1 The Mild-Infection and Prevention Sweet Spot

The HIVI pattern points to a sweet spot for herbal immunotherapy in prevention and mild-infection settings. This is probably not coincidental. Mild infection and prevention contexts feature populations who are generally otherwise well, standard-of-care interventions with modest effect sizes to improve on, and relatively low safety stakes. That combination gives herbal interventions room to demonstrate clinical value without running into the pharmacokinetic-predictability and safety-margin problems that become critical in severe-infection settings. The strong preventive-immunoprophylaxis evidence for upper-respiratory infection is real and clinically useful; it should neither be oversold (effect sizes are modest) nor dismissed (they are reproducible across independent trials).

5.2 Where Caution Is Warranted

Severe-infection adjunctive use (H4) is the single area where the literature supports explicit caution rather than enthusiasm. Herbal pharmacokinetics are less predictable than conventional-drug

pharmacokinetics at the best of times, and in critical-care settings that unpredictability can matter clinically. Chronic-infection immunomodulation (H3) is a separate story: some applications, like silymarin in hepatitis, have strong evidence bases and are reasonably well-established as adjunctive options. Others - HIV adjunctive herbal use, particularly with uncontrolled St John's wort use - have documented interaction risks with antiretroviral regimens that make blanket 'herbal immunotherapy' language misleading. The frame-level scoring is necessarily coarse; within-frame heterogeneity is real.

5.3 Limitations

Three limitations apply. First, the review was restricted to peer-reviewed English-language publications; important clinical-trial literature in Chinese, Hindi and other languages was under-represented. Second, publication bias toward positive findings is substantial in the COVID-19 antiviral-adjunct literature in particular, where publication pace outran typical peer-review standards. Third, within-frame heterogeneity is genuinely large, particularly within H3 and H1; frame-level HIVI scoring should be read as a useful summary rather than as a replacement for per-intervention clinical evidence review. These are addressable gaps rather than fatal objections.

6. Conclusion

6.1 Key Findings

Across 94 peer-reviewed studies, antiviral mechanisms (H1, HIVI 0.852) and preventive immunoprophylaxis (H5, HIVI 0.814) emerged as the two best-validated herbal immunotherapy frames. Chronic-infection immunomodulation (H3) and antibacterial approaches (H2) sit in the middle of the ranking with real but more variable evidence. Severe-infection adjunctive use (H4) scored lowest, reflecting genuine safety caution and absence of convincing clinical-endpoint evidence in critical-care populations. Effect sizes across preventive and mild-infection contexts are modest but reproducible, and position herbal immunotherapy as a legitimate adjunctive option in selected contexts rather than as either a primary therapy or an indiscriminate add-on.

6.2 Recommendations

Three recommendations follow. First, clinical guidelines should explicitly support herbal immunotherapy in preventive and mild-infection contexts where the evidence base is adequate, with named-preparation and dose specifications

rather than generic recommendations that invite product-to-product variability. Second, severe-infection use should continue to be approached with conservative evidence standards and explicit attention to herb-drug interaction risk, because the safety margin is narrower and the potential for harm correspondingly larger. Third, chronic-infection immunomodulation needs intervention-specific clinical guidance rather than frame-level recommendations, because within-frame heterogeneity is too large for useful single-message guidelines. The HIVI rubric and the full study inventory are available from the corresponding author.

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Declarations

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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-immunotherapy products.

Data Availability Statement

The full study inclusion log, frame classification records, and the HIVI 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 mechanistic and clinical 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/HIVI13) prior to the start of screening.

Appendix A

HIVI Scoring Rubric and Application-Frame Classification

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