



Drug Interactions with Herbal Remedies: A Pharmacological Analysis

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ABSTRACT

In integrative medicine, herb-drug interactions (HDIs) pose a serious therapeutic dilemma, especially in light of the growing concurrent use of conventional medications and herbal therapies. Pharmacokinetic (PK) and pharmacodynamic (PD) mechanisms are summarized, common and clinically relevant examples (such as Ayurvedic herbs in the Indian context) are highlighted, evidence levels are assessed, and risks, preventative measures, and new solutions—like blockchain for herbal quality control—are discussed. In order to maximize safety and therapeutic outcomes, data from systematic reviews, clinical research, and pharmacovigilance sources highlight the necessity of increased awareness, patient disclosure, and multidisciplinary monitoring. There are gaps in high-quality human trials and regulatory harmonization, and further research employing omics and AI techniques is suggested.

Keywords: Herb-drug interactions (HDIs), Integrative medicine, multidisciplinary, Pharmacovigilance, harmonization.

INTRODUCTION

Over 80% of people worldwide utilize herbal medicines (HMs), particularly in developing nations like India where Ayurveda—which is governed by AYUSH—is essential to healthcare. Roughly 70% of people who use herbal medicines also take conventional medications, frequently without telling their doctors. This polypharmacy raises the risk of HDI, which can result in toxicity, lengthy hospital stays, therapeutic failure, or even death. Patient non-disclosure, inconsistent herbal quality, and inadequate pharmacovigilance systems for botanicals are the main causes of underreporting. Due to multi-component herbs and the prevalence of chronic diseases, the combination of traditional Ayurvedic formulations with allopathic medications (such as anticoagulants, antidiabetics, and antiretrovirals) in India raises concerns.

For ages, traditional medical systems including Ayurveda, Traditional Chinese Medicine, and Unani have used herbal remedies. Herbal products are becoming more and more popular worldwide and are frequently used in conjunction with conventional medications. Herbal medications have drawbacks and interactions despite their advantages.

HDIs are categorized as either PD (additive, synergistic, or antagonistic actions at target locations) or PK (alterations in absorption, distribution, metabolism, excretion, or ADME). For some (like St. John's wort), the evidence is robust; for others, it is mainly preclinical.

Recent Epidemiological and Regulatory Context (2023–2025)

The use of herbal remedies is growing worldwide, and 50–70% of users also take conventional drugs. Ayurvedic polyherbal remedies are widely used in India to treat

chronic illnesses like diabetes, arthritis, and mental health issues, which increases the chance for HDI. Underreporting, unreliable standardization, and varying herbal quality (adulteration, heavy metals) are the main healthcare issues highlighted by recent mini-reviews. There is still little pharmacovigilance, particularly with regard to botanicals. Research from 2025 highlights that while quality problems (such as batch variability) make forecasting more difficult, uncontrolled or poorly standardized products increase dangers. Public awareness is at best mediocre; polls (such as those conducted in Saudi Arabia) reveal that only 11–30% of people are well knowledgeable about particular HDIs; similar trends are probably present in India

Mechanisms of Herb-Drug Interactions Pharmacokinetic Mechanisms

Herbs mostly affect medication ADME through transporters including P-glycoprotein (P-GP) and cytochrome P450 (CYP) enzymes, particularly CYP3A4, 2C9, 2D6, and 1A2, which account for around half of drug metabolism.

Absorption: GI pH/motility changes or complex formation (e.g., high-Fiber herbs limit bioavailability).

Metabolism: Inhibition (higher levels, toxicity) or induction (lower drug levels, therapeutic failure). Hyperforin from St. John's wort significantly increases P-GP and CYP3A4. Ginseng and garlic can both stimulate and inhibit.

- Distribution/Excretion:** Modified renal clearance or protein binding (licorice, for example, causes Hypokalemia through renal effects)

Pharmacodynamic Mechanisms

Direct receptor or pathway interactions:



- Synergistic or additive (for example, the antiplatelet action of garlic increases the bleeding caused by warfarin).
- Antagonistic, such as herbs that reduce the effectiveness of drugs.
- Interaction between diseases (diabetes, for example, changes CYP activity, making HDIs worse)

Levels of evidence include controlled human studies and case reports (Levels 3–4) and in vitro/animal (Level 2). Clinical confirmation is lacking for many in vitro discoveries.

Advanced Mechanisms of HDIs Beyond basic CYP/P-gp modulation

- Epigenetic and multi-omics interaction: Herbs can affect gene expression (e.g., through miRNA or histone modification), changing drug response over time.
- Modulation of the gut microbiome: Several Ayurvedic herbs, such as triphala, change the microbiota, which has an indirect effect on drug metabolism (for example, by altering transporters with secondary bile acids).
- Herb-herb-drug triads: Polyherbal Ayurvedic formulae add complexity; for example, Shaoyao Gancao decoction (licorice + paeony) has synergistic effects for pain, but there may be antagonistic effects elsewhere.

Table 1: Common Clinical Examples

Herb	Major Mechanism	Affected Drugs (Examples)	Clinical Outcome	Evidence
Garlic	Antiplatelet + variable CYP/P-gp	Warfarin, saquinavir, tacrolimus	Increased bleeding; reduced drug levels	Monitor Blood clot closely.
St. John's Wort	CYP3A4 & P-gp induction	Cyclosporine, warfarin, digoxin, SSRIs, oral contraceptives, statins	Therapeutic failure, organ rejection, breakthrough bleeding, serotonin syndrome	Strong human data; avoid with most drugs
Goldenseal	CYP2D6/3A4 inhibition	Midazolam,	Increased toxicity	High risk; avoid concurrent use
Turmeric/ Curcumin (Haldi)	Curcumin (CYP3A4/2C9 inhibition + PD)	Warfarin, tamoxifen, chemotherapy	↑Bleeding, altered efficacy	Emerging; dose-dependent; beneficial in some adjuvants
Ashwagandha (<i>Withania somnifera</i>)	Withanolides (CYP3A4 inhibition + adaptogenic)	Chemotherapy, immunosuppressants, thyroid drugs	Potential PK enhancement or thyroid modulation	Moderate; useful adjuvant but monitor levels
Fenugreek	Hypoglycemic synergy	Sulfonylureas, metformin	Severe hypoglycemia	Common in India; monitor glucose
Shankhapushpi	CYP modulation	Phenytoin	Reduced efficacy, seizures	India-specific case reports
Ashwagandha	CYP3A4 inhibition	Chemotherapy agents	Potential enhancement or altered PK	Beneficial adjuvant but monitor
Ginkgo	Platelet inhibition	Warfarin, ibuprofen	Bleeding risk	Mixed meta-analyses; caution in surgery

▪ New Developments: Forecasting and Reduction (2024–2025)

- AI and machine learning: HDIs are predicted with increasing accuracy by AI models (e.g., graph neural networks, huge language models combined with knowledge bases like DrugBank/PharmGKB). Multi-omics data is used by modern techniques to create customized risk maps and mechanistic insights. AI could solve heterogeneous healthcare requirements in India by mapping Ayurvedic phytochemicals versus medication targets.
- Pharmacogenomics Integration: Genetic variations, such as CYP2C9*3 and SLCO1B1, alter the severity of HDI; for example, inhibitory herbs are more dangerous for poor metabolizers. For clinical questions, AI-enhanced pharmacogenomic

techniques (such as RAG-based systems) exhibit potential.

- Real-World Evidence (RWE): Underappreciated HDIs, such as bleeding incidents involving garlic and anticoagulants, are highlighted by observational research utilizing electronic health data.
 - Blockchain/Quality Tools: Developing for traceability in herbal supply chains to lower the risk of adulteration or contamination.
- ### ▪ Particular Attention: Indian Context and Ayurvedic Herbs

In India, Rasayanas (such as ashwagandha and Asparagus racemosus) are used in conjunction with allopathic medications for conditions like arthritis,



diabetes, and cancer at facilities like BSDT Ayurvedic Hospital. Interactions between herbs, drugs, and diseases—such as how diabetes affects CYP2C11—are crucial. Narrow therapeutic index medications (warfarin, digoxin, phenytoin) carry more risks. Complexity is increased by polyherbal compositions.

Pharmacovigilance is advised but underutilized under AYUSH and WHO-expanded programs. About 1 in 55 hospital admissions are impacted by HDIs, which also increase the risk of adverse outcomes in polypharmacy (particularly in older patients with chronic illnesses). Perioperative use, limited TI medications, and unreported herbal consumption are high-risk situations. Serotonin syndrome, hypoglycemia (Ayurvedic antidiabetics), hemorrhage (anticoagulants + garlic/ginkgo), or organ rejection are some of the consequences. Risks are increased by variations in herbal composition (adulteration, contamination).

▪ **Prevention of Herb-Drug Interactions**

Prevention focuses on proactive identification and patient education to reduce risks before they occur.

- **Regular Screening & Disclosure:** Only around 30% of patients willingly disclose their use of herbal supplements, therefore healthcare professionals should regularly inquire about it in a nonjudgmental manner. In primary care or EHR systems, use straightforward questionnaires or medication reconciliation tools.

- **Patient education:** Stress that "natural" is safe. Inform people of possible dangers, particularly when using medications having a limited therapeutic index (such as warfarin, digoxin, phenytoin, and antiretrovirals). One to two weeks prior to surgery, advise quitting high-risk herbs.

- **High-Risk Group Identification:** Patients with diabetes, liver or kidney illness, polypharmacy, the elderly, and perioperative cases should exercise extra vigilance.

- **Pre-Use Assessment:** Before beginning herb use, consult trustworthy databases (Natural Medicines, Stockley's Herbal Medicines Interactions). Steer clear of recognized high-risk combos (e.g., garlic/ginkgo with anticoagulants; St. John's wort with most medications).

- **New Tools:** Risk stratification matrices and AI/ML-based prediction models for point-of-care choices.

Simple Primary Care Protocol: Ask → Assess risk → Advise/monitor or avoid → Document.

▪ **Management of Herb-Drug Interactions**

Management is customized when an encounter is suspected or happens.

- **Quick Action:** If the danger is high, stop using the herb; change to a safer substitute under supervision; or modify the dosage of the medication.

- **Monitoring:**
 - o INR, glucose, and therapeutic drug levels for drugs that are impacted.
 - o Clinical indicators (serotonin syndrome, hemorrhage, hypoglycemia, and hypertension).

- **Supportive Care:** If your INR is raised, take vitamin K and treat your symptoms appropriately.

- **Multidisciplinary Approach:** Involve experts in integrative medicine, clinical pharmacology, and pharmacy. AYUSH and allopathic practitioners in India should collaborate.

- **Documentation and Reporting:** Enter information in patient files and submit reports to pharmacovigilance systems (such as WHO VigiBase or PP-ASU&H under AYUSH in India).

Key Concept: Strict avoidance is necessary for high-risk situations (like St. John's wort), but many interactions can be controlled with dose modification and careful observation rather than total avoidance.

▪ **Regulatory Aspects**

Regulation of herbal products varies globally and remains a major challenge due to their complex, multi-component nature.

India (the most pertinent context):

The Ministry of AYUSH regulates traditional Ayurvedic, Siddha, and Unani (ASU) medicines.

Under the Drugs & Cosmetics Act 1940/1945, CDSCO regulates phytopharmaceuticals (standardized extracts with at least four bioactive indicators).

GMP, quality control, pharmacovigilance (National Pharmacovigilance Programme for ASU & H Drugs), and standardization to minimize variability/adulteration are among the requirements.

Worldwide Overview:

USA: Mostly dietary supplements (no efficacy preapproval; FDA post-market surveillance).

Europe (EMA): Based on 30 years of use (15 years in the EU) and bibliographic safety data, traditional herbal medical medicines may be licensed.

Natural health products (pre-market approval + GMP) in Canada.

Other: While many nations prioritize quality, safety, and traceability, China places a strong emphasis on modernizing TCM.

New Solutions: AI in pharmacovigilance, blockchain for supply chain traceability, and harmonization initiatives (e.g., ICH M12 standards on medication interaction labeling).

Present gaps: include inconsistent quality, underreporting of adverse events, a lack of clinical data on Ayurvedic HDIs particular to India, and a need for improved AYUSH and CDSCO system integration.



▪ Conclusion and Future Directions

Conclusion: In contemporary integrative healthcare, herb-drug interactions (HDIs) present a therapeutically relevant but sometimes overlooked problem. The dangers of therapeutic failure, toxicity, adverse effects, and extended hospital stays cannot be disregarded, given that 50–70% of people worldwide use herbal medications and conventional treatments concurrently. This number is significantly greater in nations like India where Ayurvedic systems coexist with allopathy. The dual pharmacokinetic (mainly CYP450 and transporter modulation) and pharmacodynamic (additive, synergistic, or antagonistic) mechanisms underlying HDIs have been highlighted in this review, along with high-impact clinical examples (including Ayurvedic herbs unique to India like ashwagandha, bitter melon, Shankhapushpi, and Piperine), and highlighted the vital role of management through careful observation, prevention through routine screening, and regulatory frameworks targeted at quality standardization. High-risk combos must be strictly avoided, even though many interactions can still be controlled by dose modification and therapeutic medication monitoring (such as INR for warfarin). The data emphasizes that "natural" does not mean "safe," especially in light of patient non-disclosure, polyherbal formulations, and varying herbal quality. For patient safety in pluralistic healthcare environments, AYUSH and allopathic systems must improve awareness, pharmacovigilance, and interdisciplinary cooperation.

Prospective Paths:

Focused research and innovation are needed in a number of critical areas to convert current knowledge into safer integrative practice:

- **Large-Scale, Context-Specific Clinical investigations:** To validate HDIs utilizing Ayurvedic polyherbal formulations, conduct well-designed randomized controlled trials and real-world evidence (RWE) investigations, particularly in primary healthcare and Indian integrative settings. To validate screening procedures and enhance electronic health record (EHR) documentation, population-based research in PHC are desperately needed.
- **Artificial Intelligence and Predictive Modeling:** Make proactive predictions about HDIs by utilizing AI, machine learning, knowledge graphs, and huge language models. AI-powered systems can create risk maps for herb-drug combinations, analyze phytochemical data, and incorporate pharmacogenomics (such as CYP variations) for customized alarms. Real-time signal identification can be made possible by integrating AI into the AYUSH pharmacovigilance program in India, such as Ayush Suraksha, to change safety monitoring from reactive to predictive.
- **Multi-Omics and Mechanistic Research:** To clarify intricate herb-drug-disease connections, combine pharmacogenomics, epigenomics, metabolomics, and gut microbiome investigations. Deeper understanding of

individual variations and long-term impacts will result from this.

- **Quality Assurance and Traceability:** Increase the transparency of the herbal supply chain by integrating blockchain technology with IoT and AI to lower batch variability, adulteration, and contamination. Stricter GMP standards and harmonization of international laws (AYUSH vs. CDSCO phytopharmaceuticals) are crucial.
- **Education and Policy Integration:** Make HDI and herbal pharmacology training required in medical and AYUSH courses. Create explainable AI-powered clinical decision support systems for use at the point of care. Encourage evidence-based "whole-system" integrative research to establish India as a global leader in safe integrative medicine by bridging traditional knowledge with contemporary science.
- **Pharmacovigilance Enhancement:** Expand the WHO VigiBase partnership and strengthen national and international reporting systems, paying particular attention to herb-drug triads and vulnerable groups (elderly, cancer patients, diabetics).
 - In conclusion, awareness, technology, and cooperative governance can all help reduce HDIs. Future initiatives that integrate digital innovation, rigorous science, and regulatory harmonization will make integrative healthcare safe, efficient, and customized, ultimately increasing patient outcomes while upholding established systems.

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