

Review Article



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"SAFETY AND HERB-DRUG INTERACTIONS OF AYURVEDIC MEDHYA DRUGS USED ALONGSIDE PSYCHOTROPIC MEDICINES"

Dr. Jalpa Gandhi¹

AFFILIATIONS:

- CEO, Ira Consultancy & Research Organisation, Bhosari, Pune, Maharashtra 411026

CORRESPONDENCE:

Dr. Jalpa Gandhi

EMAIL ID: ceo@icro.co.in

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ABSTRACT:

Background: Many people with mental and neurological disorders in India use Ayurvedic Medhya drugs alongside conventional psychotropic and antiseizure medicines, often without informing their doctors. Concurrent use creates potential for pharmacokinetic and pharmacodynamic interactions, and some herbal products carry risks of their own. **Objective:** To review the safety profile of commonly used Medhya herbs and formulations, documented and potential interactions with psychotropic and antiseizure medicines, and practical measures to reduce risk. **Methods:** Narrative review of clinical reports, pharmacokinetic and in vitro studies, systematic reviews of herb-drug interactions and quality studies of Ayurvedic products. **Results:** A clinically important interaction has been reported between phenytoin and an Ayurvedic Shankhapushpi preparation, with reduced phenytoin levels and loss of seizure control. Jatamansi increased the protective index of phenytoin in rats, suggesting pharmacodynamic or pharmacokinetic synergy. Bacopa extract and some of its constituents inhibit several human cytochrome P450 enzymes in vitro. Withania somnifera altered the pharmacokinetics of a CYP1A probe drug in rats. Ashwagandha has been associated with rare liver injury and changes in thyroid function, and Centella with rare hepatotoxicity. Piperine, present in Pippali and Trikatu, inhibits CYP3A4 and P-glycoprotein. Some Ayurvedic products contain heavy metals. Additive sedation is a plausible risk when calming herbs are combined with benzodiazepines, antipsychotics or sedating antidepressants. **Conclusion:** Most Medhya herbs are well tolerated, but interactions with drugs that have narrow therapeutic ranges, particularly antiseizure medicines and lithium, and with sedatives require attention. Systematic history-taking, communication between practitioners, quality-assured products and pharmacovigilance are essential. Clinical interaction studies are urgently needed.

Keywords: herb-drug interactions; Medhya Rasayana; psychotropic drugs; antiepileptic drugs; pharmacovigilance; cytochrome P450; Ashwagandha; Bacopa; Shankhapushpi

INTRODUCTION:

Ayurvedic medicines are widely used in India for mental and neurological conditions, both alone and alongside conventional treatment. Families often seek Ayurvedic care for memory, sleep, anxiety, epilepsy and psychosis, and patients may not tell their psychiatrist or neurologist that they are taking herbal products, or may not tell their Ayurvedic practitioner about prescribed medicines. Many Medhya products are also sold without prescription as supplements.

Herbal medicines contain many biologically active compounds. These can interact with conventional drugs in two main ways: pharmacokinetic interactions, in which one substance alters the absorption, distribution, metabolism or excretion of another, and pharmacodynamic interactions, in which two substances have additive or opposing effects on the same target or system^[1,2]. Psychotropic and antiseizure medicines are particularly vulnerable because many have narrow therapeutic ranges, are metabolised by cytochrome P450 enzymes, or have central nervous system effects that can be amplified.

This review summarises the safety profile of commonly used Medhya herbs and formulations, documented and potential interactions with psychotropic and antiseizure medicines, and practical steps to improve safety.

METHODS:

Literature was identified through PubMed, Google Scholar and the Digital Helpdesk of Indian Medicine using herb–drug interaction, cytochrome P450, pharmacokinetics, hepatotoxicity, phenytoin, lithium, antidepressants, antipsychotics, benzodiazepines, Ashwagandha, Withania, Bacopa, Brahmi, Centella, Shankhapushpi, Jatamansi, Vacha and piperine. Clinical reports, pharmacokinetic studies and systematic reviews were prioritised; in vitro and animal studies were included where clinical data were lacking. This is a narrative review.

MECHANISMS OF HERB–DRUG INTERACTION:

Pharmacokinetic interactions

The most important pharmacokinetic mechanisms involve drug-metabolising enzymes, especially the cytochrome P450 (CYP) family in the liver and intestine, and drug transporters such as P-glycoprotein^[1,2]. A herb that inhibits a CYP enzyme can increase blood levels of drugs metabolised by that enzyme, risking toxicity. A herb that induces an enzyme can lower drug levels, risking loss of effect. Many psychotropic drugs are metabolised by CYP3A4, CYP2D6, CYP1A2 or CYP2C19.

Pharmacodynamic interactions

Pharmacodynamic interactions occur when a herb and a drug act on the same system. Examples relevant to mental health include additive sedation (calming herbs with benzodiazepines or sedating antipsychotics), additive serotonergic activity (herbs with serotonergic effects plus antidepressants), and opposing effects (stimulating herbs with sedatives, or herbs that alter seizure threshold with antiseizure medicines).

Interactions in Ayurvedic formulations

Ayurvedic formulations deliberately combine herbs, sometimes including bioenhancers. Piperine, the main alkaloid of black pepper and long pepper (Pippali), inhibits human P-glycoprotein and CYP3A4^[3]. Trikatu (ginger, black pepper and long pepper) is added to many formulations to enhance their effect. When such formulations are taken with conventional drugs, piperine

may also increase drug absorption and blood levels.

SAFETY PROFILES AND INTERACTIONS OF INDIVIDUAL MEDHYA HERBS:

Shankhapushpi (*Convolvulus pluricaulis*)

The most clearly documented clinical interaction involves Shankhapushpi. A study reported that an Ayurvedic Shankhapushpi preparation taken with phenytoin was associated with reduced plasma phenytoin levels and loss of seizure control in patients, and the interaction was analysed further in experimental studies^[4]. This is an important warning, because Shankhapushpi is widely used for epilepsy and memory problems, the very patients who are likely to be on antiseizure medicines.

Jatamansi (*Nardostachys jatamansi*)

In rats, an ethanol extract of Jatamansi raised the seizure threshold in the maximal electroshock model, and when combined with phenytoin it increased the protective index of phenytoin from 3.63 to 13.18^[5]. Serum phenytoin data suggested a synergistic interaction. While this may be beneficial under controlled conditions, it also shows that Jatamansi can change the effect of phenytoin, and clinical use together requires monitoring. Jatamansi is also sedating, so additive effects with sedative drugs are possible.

Brahmi (*Bacopa monnieri*)

In an in vitro study using human enzymes, a standardised Bacopa extract and some of its constituents inhibited several cytochrome P450 enzymes, including CYP2C19, CYP2C9, CYP1A2 and CYP3A4^[6]. Many antidepressants, antipsychotics and benzodiazepines are metabolised by these enzymes. In vitro inhibition does not always translate into clinical interactions, but it indicates a need for caution and for clinical pharmacokinetic studies. Bacopa commonly causes gastrointestinal side effects such as nausea and loose stools^[7].

Ashwagandha (*Withania somnifera*)

Ashwagandha is widely used for stress, anxiety and sleep. In rats, oral Withania extract given with phenacetin, a CYP1A probe drug, reduced phenacetin exposure, increased its elimination and shortened its half-life, suggesting induction of CYP1A^[8]. Human liver microsome experiments in the same study showed no direct CYP1A inhibition. CYP1A2 metabolises clozapine and olanzapine, so this finding is relevant to patients taking these antipsychotics.

Ashwagandha has also been associated with rare cases of liver injury. A case series from Iceland and the United States Drug-Induced Liver Injury Network described cholestatic or mixed liver injury attributed to Ashwagandha supplements, with recovery after stopping the product^[9]. In a randomised trial in patients with subclinical hypothyroidism, Ashwagandha increased thyroid hormone levels^[10], which may interact with thyroid medicines and is relevant to patients on lithium, which can cause hypothyroidism. Additive sedation with sedative drugs is also possible.

Mandukaparni (*Centella asiatica*)

Centella has been associated with rare cases of hepatotoxicity, with resolution after withdrawal of the product^[11]. Its potential effects on drug metabolism are less well studied. It may have additive effects with sedatives.

Vacha (*Acorus calamus*)

Vacha is used in small doses in many Medhya formulations. Some chemotypes contain beta-asarone, which has raised safety concerns in toxicological studies. Vacha may also have sedative and anticonvulsant effects in animals, so it may interact with sedatives and antiseizure medicines. The chemotype and dose should be controlled.

Sarpagandha (*Rauvolfia serpentina*)

Sarpagandha contains reserpine, which depletes monoamines

and can cause depression, hypotension and nasal congestion. It has important pharmacodynamic interactions with antidepressants, antipsychotics and antihypertensive drugs. It should be used only under medical supervision and generally avoided in patients with depression.

Summary table

Table 1: Safety issues and interactions of Medhya herbs with psychotropic and antiseizure drugs

Herb or formulation	Documented or potential issue	Relevant psychotropic or antiseizure drugs	Evidence level
Shankhapushpi preparation	Reduced phenytoin levels; loss of seizure control ^[4]	Phenytoin	Clinical report
Jatamansi	Synergy with phenytoin in rats ^[5] ; sedation	Phenytoin; sedatives	Animal
Brahmi (<i>Bacopa</i>)	Inhibits several CYP enzymes in vitro ^[6] ; GI effects ^[7]	Antidepressants, antipsychotics, benzodiazepines	In vitro
Ashwagandha	CYP1A induction in rats ^[8] ; rare liver injury ^[9] ; thyroid effects ^[10] ; sedation	Clozapine, olanzapine; lithium (thyroid); sedatives	Animal; case series; RCT
Mandukaparni (<i>Centella</i>)	Rare hepatotoxicity ^[11] ; sedation	Hepatotoxic drugs; sedatives	Case reports
Piperine (<i>Pippali</i> , <i>Trikatu</i>)	Inhibits CYP3A4 and P-glycoprotein ^[3]	Many CYP3A4 substrates (e.g., some benzodiazepines, quetiapine, carbamazepine)	In vitro and human tissue
Sarpagandha	Monoamine depletion; depression; hypotension	Antidepressants, antipsychotics, antihypertensives	Pharmacology
Metal- or mineral-containing products	Heavy metal contamination in some products ^[12]	All patients, especially long-term use	Quality survey

PRODUCT QUALITY AND CONTAMINATION:

Interactions are not the only safety concern. A study of Ayurvedic medicines sold over the internet found that about one-fifth of products contained detectable lead, mercury or arsenic, with higher rates among Rasa Shastra (metal-mineral) preparations, and similar rates in products manufactured in the United States and India^[12]. Heavy metals can cause neurological, renal and haematological toxicity and can themselves produce psychiatric symptoms. Adulteration with undeclared conventional drugs, including sedatives and steroids, has also been reported for some herbal products internationally.

The World Health Organization has published guidelines on assessing the quality of herbal medicines with reference to contaminants and on safety monitoring of herbal medicines in pharmacovigilance systems^[13,14]. Ayurvedic products used for

mental health should be sourced from manufacturers with good manufacturing practice certification and batch-specific quality testing.

PROCEDURE-RELATED RISKS: PANCHAKARMA AND PSYCHOTROPIC MEDICINES:

Interactions are not limited to oral herbs. Panchakarma procedures can change the body's fluid and electrolyte balance and drug absorption.

- **Vamana and Virechana** cause loss of fluid and electrolytes. In patients taking lithium, dehydration and sodium loss can raise lithium levels to toxic concentrations. Low potassium or magnesium can increase the risk of heart rhythm problems in patients taking antipsychotics or antidepressants that prolong the QT interval.
- **Purgation and fasting (*Langhana*)** can reduce the

absorption of oral medicines taken during the procedure period, potentially lowering antiseizure or antipsychotic levels and risking relapse.

- **Snehapana (internal oleation with large doses of medicated ghee)** may alter the absorption of fat-soluble drugs and can cause nausea and loose stools that affect drug intake.
- **Basti** with medicated oils or decoctions has unknown effects on drug absorption.

Patients on lithium, clozapine, antiseizure medicines or QT-prolonging drugs should have medical review before Shodhana procedures, with monitoring of drug levels and electrolytes where indicated, and clear plans for taking medicines during the procedure days.

PATIENT DISCLOSURE AND COMMUNICATION:

Patients often do not tell doctors about herbal products because they assume natural products are harmless, fear disapproval, or are not asked. Similarly, Ayurvedic practitioners may not always ask about prescribed medicines, or patients may stop them when starting Ayurvedic treatment. Both situations increase risk.

Simple steps can improve communication: asking routinely and without judgement; recording all products, including brand names, in both medical and Ayurvedic records; encouraging patients to bring all their medicines and supplements to appointments; and providing patients with written summaries of their treatment to share with other practitioners. Integrated clinics in which psychiatrists and Ayurvedic physicians work together can reduce these risks further.

HIGH-RISK SITUATIONS:

Based on the evidence reviewed, the following situations deserve particular attention:

- **Antiseizure medicines with narrow therapeutic ranges** (phenytoin, carbamazepine, valproate): risk of reduced or increased drug levels and seizure breakthrough or toxicity. Monitor drug levels when starting or stopping herbal products.
- **Lithium:** narrow therapeutic range; dehydration from Panchakarma procedures (Vamana, Virechana) or diuretic herbs can raise lithium levels to toxic concentrations. Thyroid effects of herbs should also be considered.
- **Clozapine and olanzapine:** CYP1A2 substrates; induction or inhibition can change levels. Clozapine levels are clinically important.
- **Benzodiazepines, Z-drugs and sedating antipsychotics:** additive sedation with calming herbs.
- **Antidepressants:** potential CYP interactions; pharmacodynamic effects of herbs with serotonergic or monoaminergic activity.
- **Patients with liver disease** or taking other hepatotoxic drugs (such as valproate): avoid or monitor herbs associated with liver injury.
- **Pregnancy and breastfeeding:** limited safety data for most Medhya herbs.
- **Children and older adults:** dose adjustment and greater vulnerability to adverse effects.

PRACTICAL RECOMMENDATIONS:

For Ayurvedic practitioners

1. Ask every patient about all prescribed medicines, over-the-

counter products and supplements, and record them.

2. Avoid stopping or changing psychotropic or antiseizure medicines; refer back to the prescribing doctor for any change.
3. Prefer single herbs or simple formulations with known composition when patients are on high-risk drugs.
4. Be cautious with formulations containing piperine, Sarpagandha or metals in such patients.
5. Advise patients to report jaundice, dark urine, itching, unusual drowsiness, confusion, tremor or seizure breakthrough promptly.
6. Report suspected adverse reactions to the national AYUSH pharmacovigilance programme.

For psychiatrists and neurologists

1. Ask specifically about Ayurvedic and herbal products, in a non-judgemental way, because patients may not volunteer this information.
2. Consider herbal products when drug levels change unexpectedly or new adverse effects appear.
3. Monitor drug levels, liver function and thyroid function where relevant.
4. Communicate with the patient's Ayurvedic practitioner where possible.

For researchers and regulators

1. Conduct clinical pharmacokinetic interaction studies for the most commonly co-used Medhya herbs and psychotropic drugs, using probe drug cocktails and therapeutic drug monitoring.
2. Include systematic adverse event reporting in all Ayurvedic clinical trials.
3. Strengthen quality control and post-marketing surveillance of Medhya products.
4. Develop interaction monographs in pharmacopoeias and clinical guidance for practitioners.

DISCUSSION:

Most Medhya herbs have good safety records in clinical trials and long traditional use. The risks discussed in this review do not mean that Ayurvedic and conventional treatments cannot be combined; integrated care is common and often valued by patients. However, safe integration requires awareness that herbs are pharmacologically active and can change the effects of conventional drugs.

The evidence base on interactions is thin. Most data come from in vitro and animal studies, case reports and theoretical considerations. Only one well-known clinical report concerns a Medhya preparation and an antiseizure drug, and it is now three decades old. Clinical interaction studies in patients taking commonly used combinations, such as Ashwagandha with antidepressants or Brahmi with antiepileptic drugs, are urgently needed. Until such data exist, a cautious approach combining careful history-taking, monitoring and communication is the most appropriate.

Pharmacovigilance is essential. India has established a national pharmacovigilance programme for Ayurveda, Siddha, Unani and Homoeopathy drugs. Practitioners, patients and manufacturers should be encouraged to report adverse events, including suspected interactions, so that signals can be detected and investigated.

CONCLUSION:

Medhya herbs are widely used alongside psychotropic and antiseizure medicines. Documented and potential interactions include reduced phenytoin levels with Shankhapushpi, synergy between Jatamansi and phenytoin, CYP inhibition by Bacopa, CYP induction by Ashwagandha in animals, enzyme and transporter inhibition by piperine, and additive sedation. Rare liver injury and thyroid effects with Ashwagandha, hepatotoxicity with Centella and heavy metal contamination in some products are further concerns. Careful history-taking, quality-assured products, monitoring, interprofessional communication, pharmacovigilance and clinical interaction studies are needed to ensure that integrated care is safe.

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