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"HERB–DRUG INTERACTIONS OF COMMONLY USED AYURVEDIC DRUGS: A CRITICAL REVIEW OF HUMAN EVIDENCE, MECHANISMS AND THE CLASSICAL CONCEPT OF SAMYOGA"

Dr. Jalpa Gandhi[1]

AFFILIATIONS:
1. CEO, Ira Consultancy & Research Organisation, Bhosari, Pune, Maharashtra 411026

CORRESPONDENCE:
Dr. Jalpa Gandhi
EMAIL ID:
ceo@icro.co.in

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ABSTRACT
Many patients in India take Ayurvedic medicines alongside conventional drugs, often without telling either prescriber. Herb–drug interactions are therefore a practical concern for integrative care, yet the evidence is scattered across pharmacology, clinical pharmacology and case literature. This critical review summarises human evidence for interactions involving commonly used Ayurvedic drugs, examines their mechanisms, and relates them to the classical Dravyaguna concepts of samyoga (combination), yogavahi (a carrier that enhances other substances) and viruddha (incompatibility). Human pharmacokinetic or clinical evidence was found for seven drugs. Piperine, the principal alkaloid of Pippali and Maricha, increased exposure to phenytoin, propranolol and theophylline in volunteers, consistent with its inhibition of CYP3A4 and P-glycoprotein. Gugulipid reduced peak concentrations and exposure of propranolol and diltiazem, and guggulsterone activates the pregnane X receptor, which induces CYP3A. Garlic supplements halved saquinavir exposure. Two studies of curcumin with talinolol reported opposite effects. Case reports describe altered response to phenytoin with Shankhapushpi, to chlorpropamide with karela, and to warfarin with a fenugreek-containing product. For Ashwagandha, in vitro inhibition of major cytochrome P450 enzymes was weak, but its effect on thyroid hormones and rare liver injury raise pharmacodynamic concerns. Most evidence is from small, short studies of single compounds rather than classical formulations. We propose practical guidance for drugs with a narrow therapeutic index and a research agenda centred on realistic doses of classical preparations.

KEYWORDS: Herb–drug interaction, Ayurveda, piperine, cytochrome P450, P-glycoprotein, Dravyaguna, pharmacovigilance

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INTRODUCTION

Ayurvedic medicines are widely used in India alongside conventional drugs, by patients with chronic disease and by people seeking prevention. Concurrent use is often hidden: in a survey of cancer patients at a tertiary centre in Kerala, about a third used traditional or complementary medicine, and 71% of users had not told their treating physicians.[1] When neither prescriber knows the full list of what a patient is taking, an interaction may go unrecognised and be misattributed to disease progression, treatment failure or a new adverse reaction.

Herb–drug interactions can be pharmacokinetic, when a herb changes the absorption, distribution, metabolism or excretion of a drug, or pharmacodynamic, when the herb adds to or opposes the drug's effect.[2] The most studied pharmacokinetic pathways are the cytochrome P450 (CYP) enzymes, notably CYP3A4, and the efflux transporter P-glycoprotein, which together determine the oral bioavailability of a large share of medicines; regulators require new drugs to be evaluated for these interactions.[3] Botanical products have not been held to the same standard.

Dravyaguna has its own vocabulary for these questions. The classical texts hold that the action of a substance depends on its combination (samyoga) with others, describe honey as yogavahi, a carrier that takes on and enhances the properties of what it is combined with, and list combinations that are harmful although each component is wholesome alone (viruddha).[4] These ideas are not identical to modern pharmacokinetics, but they show that classical practice expected the effect of a drug to change in combination. This review summarises human evidence for interactions involving commonly used Ayurvedic drugs, outlines their mechanisms, and draws practical and research conclusions.

METHODS

This is a critical narrative review. We searched PubMed, PubMed Central, publisher websites and drug interaction resources for human studies and case reports of interactions between conventional drugs and Ayurvedic drugs in common use, including Pippali (*Piper longum*), Maricha (*Piper nigrum*), Guggulu (*Commiphora wightii*), Haridra (*Curcuma longa*), Lashuna (*Allium sativum*), Shankhapushpi, Karavellaka (*Momordica charantia*), Methika (*Trigonella foenum-graecum*) and Ashwagandha (*Withania somnifera*). Search terms combined each drug name with interaction, pharmacokinetics, bioavailability, cytochrome P450, P-glycoprotein and case report. Human pharmacokinetic studies and clinical reports were given priority; in vitro and animal studies were included only to explain mechanisms.

HUMAN EVIDENCE BY DRUG

The human evidence is summarised in Table 1. It is dominated by small, short studies in healthy volunteers using isolated constituents or single-herb products, supplemented by case reports.

Pippali and Maricha

Piperine, the main alkaloid of long pepper and black pepper, is the best-studied Ayurvedic constituent in interaction research. In healthy volunteers it increased the absorption of phenytoin after a single dose,[5] and pepper added to soup altered phenytoin absorption and elimination in a second study.[6] The same research group reported enhanced bioavailability of propranolol and theophylline.[9] Mechanistic work showed that piperine inhibits P-glycoprotein-mediated transport of digoxin and cyclosporine in intestinal cell monolayers and inhibits CYP3A4 in human liver microsomes, which together can raise the plasma concentration of orally given substrates.[8] A recent systematic review of food and herb interactions with phenytoin rated the piperine studies as low or very low certainty because of their size and design, but still advised monitoring phenytoin concentrations when the two are combined.[7]

These findings are relevant to Dravyaguna because Pippali and Trikatu are added to many classical formulations, and modern authors often describe them as bioenhancers. The same action that may improve the absorption of co-administered herbs can raise the levels of a conventional drug with a narrow therapeutic index

Guggulu

In randomised crossover studies in healthy men, gugulipid significantly reduced the peak concentration and the area under the curve of propranolol and diltiazem, and the authors warned that this could lead to non-response in patients taking these drugs.[10] Guggulsterone activates several nuclear receptors, including the pregnane X receptor, and induces CYP3A gene expression,[11] which provides a second mechanism by which Guggulu preparations could lower exposure to CYP3A substrates.

Table 1. Human evidence for interactions between commonly used Ayurvedic drugs and conventional medicines.

Ayurvedic drug	Conventional drug	Evidence and finding	Probable mechanism
Pippali, Maricha (piperine)	Phenytoin	Single-dose studies in 5 and 6 volunteers: increased absorption and, with pepper in food, delayed elimination;[5,6] graded very low certainty in a 2026 systematic review[7]	Inhibition of CYP3A4 and P-glycoprotein[8]
Pippali, Maricha (piperine)	Propranolol, theophylline	Volunteer study reporting enhanced bioavailability[9]	As above
Guggulu (gugulipid)	Propranolol, diltiazem	Randomised crossover studies in 10 and 7 healthy men: significantly lower Cmax and AUC[10]	Reduced absorption; PXR activation and CYP3A induction by guggulsterone[11]
Haridra (curcumin)	Talinolol	Two volunteer studies with opposite results: reduced bioavailability;[12] AUC increased by 67–81%, greatest in ABCB1 TT genotype[13]	P-glycoprotein modulation; genotype-dependent
Lashuna (garlic supplement)	Saquinavir	9 volunteers: AUC fell by about half and Cmax by 54%; still 35% below baseline after 10-day washout[14]	Induction of intestinal CYP3A4 and/or P-glycoprotein
Lashuna (garlic supplement)	Warfarin	No pharmacodynamic interaction in healthy subjects[15]	—
Shankhapushpi preparation	Phenytoin	Clinical observation with confirmatory analysis[16]	Not established
Karavellaka (karela)	Chlorpropamide	Case report (letter) of altered glycaemic response[17]	Additive hypoglycaemic effect (pharmacodynamic)
Methika (in a boldo–fenugreek product)	Warfarin	Case report of raised INR[18]	Coumarin content; pharmacodynamic
Ashwagandha	Thyroid drugs (theoretical)	Randomised trial: T3 and T4 rose and TSH fell over 8 weeks in subclinical hypothyroidism[19]	Pharmacodynamic effect on thyroid function

Haridra

Curcumin illustrates how difficult interactions are to predict. One study in Chinese volunteers found that curcumin unexpectedly reduced the bioavailability of the P-glycoprotein substrate talinolol,[12] whereas a later randomised crossover study in 18 volunteers, stratified by ABCB1 genotype, found that 1000 mg of curcumin daily for 14 days increased talinolol exposure by 67–81% and reduced its clearance by about a quarter, with the largest effect in the TT genotype.[13] Differences in dose, duration and genotype probably explain the discrepancy. The practical lesson is that a single study, in either direction, should not be taken as proof that an interaction does or does not occur.

Lashuna

In nine healthy volunteers, garlic supplements taken twice daily for three weeks reduced overall saquinavir exposure by about half and peak concentration by 54%, and levels remained about 35% below baseline ten days after garlic was stopped.[14] The persistence after withdrawal suggests enzyme or transporter induction rather than a simple effect on absorption. By contrast, a controlled study found no pharmacodynamic interaction between garlic and warfarin in healthy subjects.[15] Garlic therefore shows that the same herb can interact with one drug and not another, depending on the pathway each drug

uses.

Shankhapushpi, Karavellaka and Methika

Three drugs are supported by case-level evidence. An analysis of a clinically important interaction between phenytoin and a Shankhapushpi preparation was reported from Mumbai in 1992,[16] and is often cited because both phenytoin and Shankhapushpi are used in neurological disorders. A letter in the Lancet described an interaction between karela and chlorpropamide,[17] consistent with the additive hypoglycaemic action expected when Karavellaka is taken with antidiabetic drugs. A case of raised INR in a patient on warfarin who took a product containing fenugreek and boldo has also been reported;[18] coumarin constituents in both herbs are the suggested mechanism.[2]

Ashwagandha

Ashwagandha is widely used and often combined with conventional drugs, but human pharmacokinetic interaction data are lacking. In human liver microsomes, an aqueous extract inhibited CYP3A4, CYP2C8 and CYP2D6 only at concentrations above 100 μg/mL, which the authors interpreted as a low risk of metabolic interaction.[20] The concern is pharmacodynamic. In a randomised placebo-controlled trial in subclinical hypothyroidism, 600 mg of root extract daily for eight weeks raised T3 and T4 and lowered TSH,[19] so additive or opposing effects with levothyroxine or antithyroid drugs are plausible. Ashwagandha has also been associated with cholestatic liver injury, sometimes severe in people with pre-existing liver disease,[21,22] which is relevant when it is combined with other potentially hepatotoxic drugs.

MECHANISMS AND THEIR LIMITS

The interactions in Table 1 fall into four groups. The first is inhibition of CYP3A4 and P-glycoprotein, which raises drug exposure, as with piperine.[8] The second is induction through nuclear receptors such as the pregnane X receptor, which lowers exposure and persists after the herb is stopped, as suggested for guggulsterone and garlic.[11,14] The third is altered absorption by binding, motility or solubility, which may contribute to the effect of gugulipid.[10] The fourth is pharmacodynamic addition or opposition, as with Karavellaka and antidiabetic drugs, fenugreek and anticoagulants, or Ashwagandha and thyroid function.[17–19]

Extrapolating these mechanisms to practice is difficult. Most experiments used isolated compounds such as piperine or curcumin rather than the whole plant or a classical formulation, in which the dose of each constituent is much lower and other constituents may modify absorption. In vitro inhibition constants do not translate directly into clinical risk without information on concentrations reached in the gut and liver, which is the approach regulators use for new drugs[3] and which was not possible for whole extracts in the Ashwagandha study.[20] Human studies were mostly single-dose or short and enrolled few healthy young men, whereas real patients are older, take several drugs and use herbs for months.

A DRAVYAGUNA PERSPECTIVE

Classical texts treat combination as a determinant of action. A drug's effect is understood to depend on samyoga, on the vehicle with which it is given (anupana), and on the person and condition. The description of honey as yogavahi[4] expresses the idea that a carrier can amplify what it accompanies, and Pippali and Trikatu are used in exactly this role in many formulations. Modern findings on piperine give a mechanistic basis to this classical intention, but they also show its other side: an enhancer does not discriminate between a co-administered herb and a co-administered antiepileptic or immunosuppressant.

The doctrine of viruddha, which lists combinations that are harmful although each component is wholesome,[4] shows that classical authors recognised that incompatibility arises from combination rather than from any single substance. Herb–drug interaction is a modern instance of the same principle. Framing it in this way may help Ayurveda practitioners accept interaction checking as part of their own tradition rather than as an external restriction, and may help conventional clinicians see that the Ayurveda prescriber has a vocabulary for discussing it.

PRACTICAL GUIDANCE

The level of caution should follow the therapeutic index of the conventional drug and the strength of the evidence. Table 2 sets out a pragmatic approach.

Separating the times of administration may reduce interactions that act through binding in the gut, but it does not prevent those that act through enzyme induction or systemic inhibition, which persist for days.[14] Suspected interactions should be reported to the national pharmacovigilance programme for Ayurveda, Siddha, Unani and Homoeopathy drugs, with the product name, batch, dose and timing recorded.

Table 2. Pragmatic guidance for co-prescription of Ayurvedic and conventional medicines.

Situation	Suggested action
Narrow therapeutic index drugs: phenytoin, warfarin, digoxin, theophylline, cyclosporine, tacrolimus, antiretrovirals, lithium	Avoid starting or stopping Pippali, Trikatu, Guggulu, Lashuna supplements or high-dose Haridra extracts without monitoring drug levels or INR; record the formulation and dose
Antidiabetic drugs with Karavellaka, Methika or similar	Expect additive glucose lowering; monitor glucose more often and adjust doses jointly
Anticoagulants and antiplatelet drugs	Monitor INR when fenugreek-containing or other coumarin-rich products are added[18]
Thyroid drugs with Ashwagandha	Check thyroid function after starting or stopping Ashwagandha[19]
Pre-existing liver disease or other hepatotoxic drugs	Use Ashwagandha and other herbs with reported liver injury cautiously and monitor liver tests[21,22]
All patients	Ask about Ayurvedic and other traditional medicines at every visit and record them in the medication list[1]

RESEARCH PRIORITIES

- Clinical pharmacokinetic studies of classical formulations at their usual doses, rather than of isolated compounds at pharmacological doses.
- Use of validated probe-drug cocktails to measure the effect of commonly used formulations on several CYP enzymes and transporters at once.
- Physiologically based pharmacokinetic modelling to predict which interactions are likely to matter clinically, as regulators require for new drugs.[3]
- Studies in patients rather than young healthy volunteers, including older adults and people with polypharmacy.
- Interaction fields in Ayurveda pharmacovigilance reporting forms, and inclusion of Ayurvedic drugs in hospital drug interaction databases.

8. LIMITATIONS

This is a narrative review, and relevant studies in regional journals or in languages other than English may have been missed. The available human studies are small, and several important reports are old letters or case reports whose full details are not easily accessible. Absence of evidence for an interaction should not be read as evidence of safety, since most Ayurvedic drugs have never been tested.

9. CONCLUSION

Human evidence shows that several commonly used Ayurvedic drugs can alter the exposure to, or the effect of, conventional medicines. The clearest examples are piperine from Pippali and Maricha, which raises drug levels, and Guggulu and garlic, which lower them. The evidence base is thin and mostly derived from isolated compounds, so the clinical importance of interactions with classical formulations at usual doses remains largely unknown. Until better data exist, practitioners of both systems should ask about and record all medicines, take particular care with drugs that have a narrow therapeutic index, and report suspected interactions. The classical principle that the action of a drug depends on its combination provides a natural place for interaction checking within Ayurvedic practice.

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