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Un-Reported Herbal and Drug Interactions: A Threat to Ponder for Patients' Safety in Pakistan

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ABSTRACT

Pakistan uses a lot of herbal remedies because of economic, religious, and cultural reasons. Despite their widespread use, there is a considerable danger of drug–herbal interactions (DHIs) when they are used with prescription medications. Hospitalizations, severe adverse drug reactions (ADRs), and changed medication efficacy can result from these combinations. With an emphasis on widely used herbs like black seed, fenugreek, ginger, liquorice, garlic, neem, ajwain, green tea, and ashwagandha, this review examines the extent of DHIs in Pakistan. In this review article, it is highlighted that there are clinically important interactions with anticoagulants, antidiabetic, and cardiovascular medications, talk about its pharmacodynamic and pharmacokinetic mechanisms, and ponder the weaknesses in Pakistan's National pharmacovigilance center (NPC). To reduce these dangers, we make suggestions for research, legislation, and therapeutic practices. As far as we are aware, this is the first comprehensive review paper on DHIs that is tailored to Pakistan.

Keywords: *DHIs, Hypoglycemia, Pakistan National pharmacovigilance center, warfarin, blackseed, fenugreek.*

INTRODUCTION

Herbal and traditional remedies are widely used in Pakistan and are considered to be "natural and safe" due to their cultural roots. Across age groups and geographical areas, surveys and KAP studies indicate significant concurrent usage with allopathic medications, which provides an environment that is conducive to DHIs that are rarely reported in local literature [1].

The translation of worldwide DHI statistics to Pakistani practice necessitates consideration of local herb choices, market formulations, and illness burdens (e.g., diabetes, Cardiovascular diseases (CVD) and TB). In our context, high-risk drug classes include digoxin, thyroid hormone, insulin/oral antidiabetics, antihypertensives, antiarrhythmics, warfarin/DOACs, and antiplatelets drugs with substantial

pharmacodynamic liabilities or restricted therapeutic indices. Although systematic capture of herbal DHIs is still in its infancy, the Pakistan National Pharmacovigilance Centre (NPC) at Drug regulatory authority of Pakistan (DRAP) currently offers online Med Vigilance e-Reporting for ADRs/AEs [2].

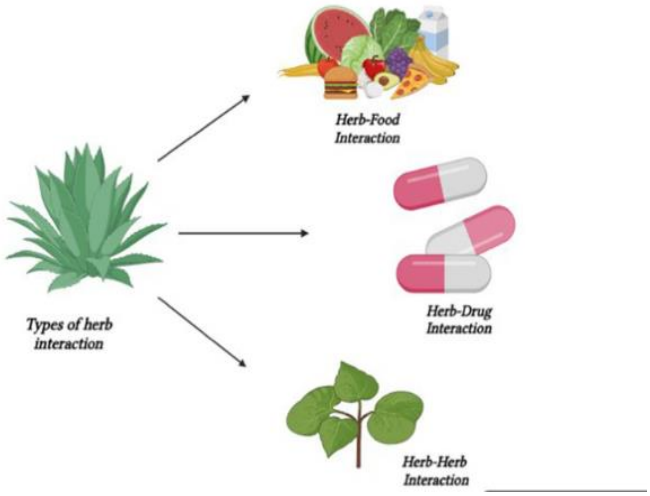

Figure 1: Herbal-Drug Interaction [3].

METHODOLOGY (A NARRATIVE REVIEW APPROACH)

In the absence of clinical evidence, the information for mechanistic plausibility and human data (randomised trials, observational studies, case reports, systematic reviews) using PubMed/PMC and reliable sources. Priority herbs selected according to Pakistani consumption records and availability: Nigella sativa (black seed), fenugreek (methi), licorice (mulathi), neem (Azadirachta indica), ashwagandha (Withania somnifera), ajwain (Trachyspermum ammi), ginger, garlic, and green tea. For local reporting procedures, we also looked over DRAP/WHO pharmacovigilance materials [4-6].

Pharmacovigilance and Herbal Use according to Pakistan's Context

Numerous surveys conducted in Pakistan show a high incidence of herbal use and favorable opinions about its safety, which are frequently influenced by family and the internet rather than medical professionals. These factors can lead to DHIs that go unnoticed [1].

The Med Vigilance e-Reporting web platform and reporting forms are available through the National Pharmacovigilance Centre of DRAP. Despite Pakistan's 2018 admission to the WHO Program for International Drug Monitoring, publications highlight inconsistent system maturity and underreporting, especially for supplemental drugs. This discrepancy likely obscures real-world DHI emissions [6, 7].

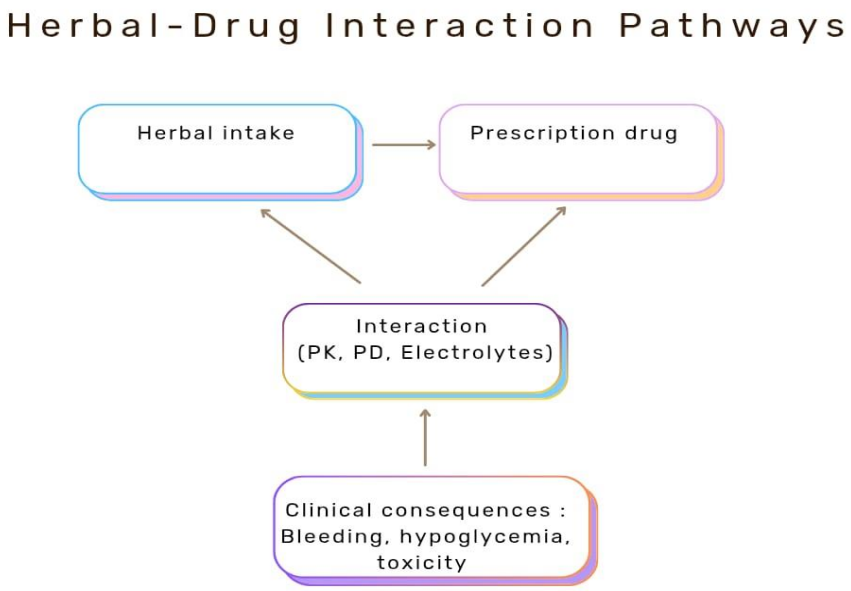

Figure 2: Herbal Drug Interaction Pathways.

HERBAL-DRUG INTERACTIONS AT HIGH PRIORITY IN PAKISTAN

Antiplatelets and Anticoagulents

Camellia sinensis (Green Tea) with Warfarine

A well-known case study shows that consuming a lot of green tea (between ½ and 1 gallon per day) decreased INR; after stopping, INR returned to normal. Although minimal intake is safe in most cases, vigilance is necessary [8-10].

Fenugreek/Ginger with Warfarine

There is conflicting evidence. Although isolated cases (including ginger tea) reported ↑INR, systematic reviews show little clinical evidence that ginger improves the warfarin effect. Additionally, case reports have connected fenugreek in combination with warfarin (with boldo) to ↑INR. When initiating or terminating high-dose supplements, check INR and counsel patients on bleeding symptoms [11-13].

Antiplatelets Effect of Trachyspermum ammi (Ajwain)

Despite the lack of clinical human scientific evidence, Pakistani research (both experimental and animal) suggests that aspirin/clopidogrel has mild antithrombotic and antiplatelet properties that, if widespread, could exacerbate bleeding. Mark should be taken seriously as a possible threat [14-16].

Systematically enquire about high-volume green tea, ginger/fenugreek supplements, and ajwain-based treatments for patients taking warfarin, DOACs, or dual antiplatelet therapy; modify monitoring as necessary.

CARDIOVASCULAR DRUGS: ANTIHYPERTENSIVES, DIURETICS, AND DIGOXIN

Diuretics/Digoxin with Glycyrrhiza glabra (Licorice)

There are human case reports of liquorice (glycyrrhizin) causing hypokalaemia, which increases the risk of digoxin toxicity and intensifies diuretic-induced K+ loss. Chronic usage of candy or liquorice tea can also be hazardous [17, 18].

Antihypertensives/Antiplatelets with Garlic/Ginger

Antiplatelet effects are suggested by lab and clinical data; interactions between hypertension and antihypertensive medications are conceivable through vasodilatory or blood pressure-lowering effects, however the quality of the evidence varies. When using high-dose supplements in polypharmacy, exercise care [19].

METABOLIC THERAPIES AND ENDOCRINE

Fenugreek/black seed/Neem with Antidiabetics

Fenugreek and Nigella sativa have been shown in human trials and reviews to have glucose-lowering properties, while neem has been shown to have animal/human signals that suggest additive hypoglycemia with insulin or sulfonylureas. Advise patients who add or remove these herbs to follow SMBG/CGM uptitration regimens [20, 21].

Withania sominifera (Ashwagandha) with Thyroid Axis

According to several case reports, ashwagandha may cause thyrotoxicosis by stimulating the production of thyroid hormones or by including exogenous hormone in contaminated products. Advise patients using levothyroxine or at risk for arrhythmias not to take ashwagandha unattended [22, 23].

MECHANISMS

Pharmacodynamic Activity

- **High risk of bleeding:** Herbs with antithrombotic and antiplatelet qualities (garlic, ginger, and ajwain—limited human data) combined with antiplatelets and warfarin [12].
- **Hypoglycemia:** Insulin/sulfonylureas, neem, black seed, and fenugreek [21].

Pharmacokinetic Modulation

- **Vitamin K antagonism:** Warfarin may be adversely affected by excessive consumption of green tea (dietary vitamin K and other variables) [8].
- **Transporter/Enzyme effect:** Though its clinical importance is unknown, ashwagandha exhibits varying in vitro effects on CYP3A4/2B6, whereas thymoquinone (black seed) exhibits CYP2C9 suppression in vitro => potential warfarin interaction [24, 25].

Electrolytic Imbalance

- **Hypokalaemia by Licorice:** Intensifies the negative effects of diuretics and digoxin toxicity [17].

Most Specific Herbs Usage in Pakistan

Herbs	Interactions	Evidence
Ajwain	Theoretically increased bleeding when taken with anticoagulants/antiplatelets	No human clinical data present but animal data in Pakistan [14].
Ashwagandha	Cause thyrotoxicosis. Must be taken with cautions with thyroid meds and sedatives	Multiple human cases have been reported [23, 26].
Neem (azadirachta)	Causes hypoglycaemia with antidiabetics	Animal and human studies and data available [27, 28].
Kalonji (Black seed)	CYP2C9 inhibition with warfarin and hypoglycemic effect with antidiabetics	Invitro studies upon human glucose [21, 24].
Licorice (mulathi)	Causes diuretic potassium loss and digoxin toxicity causes hypokalaemia	Human cases data available[29].
Fenugreek (methi)	Increased INR with warfarin, decreased glucose with antidiabetics	Case studies and human antidiabetic trials; track glucose and INR [11, 13].
Ginger (adrak)	Increased bleeding risk with antiplatelets/anticoagulants.	RCT PK studies reveal no effect at normal doses; caution with high-dose supplements; mixed data; 1–few case signals [12].
Green Tea	Decreased INR if taken in high quantity with warfarin	Human cases have been reported[8, 9].

CLINICAL SCENARIOS IN PAKISTAN

Atrial Fibrillation on Green Tea and Warfarin

- **Risk:** inadequate anticoagulation in the event that intake abruptly rises.
- **Action:** Encourage regular consumption; if there are dietary changes, reassess the INR [30].

Heart Failure with Digoxin, Daily Licorice Consumption, and Loop Diuretic

- **Risk:** Digoxin toxicity (e.g., nausea, arrhythmias) following hypokalaemia.
- **Action:** Steer clear of liquorice and keep a close eye on renal and K+ function [29].

Type 2 Diabetes: Fenugreek Capsules with Insulin

- **Risk:** Nighttime lows and additive hypoglycemia during Ramadan.

- **Action:** Intensification of SMBG/CGM, dose modifications, and nutritional consultation [21].

Hyperthyroidism on Ashwagandha with Levothyroxine

- **Risk:** Arrythmia and thyrotoxicosis precipitation.
- **Action:** If already utilized, think about TSH/T4 monitoring instead [23].

Pakistan's Necessary Step Needed upon Pharmacovigilance and its Policy

Several necessary steps that Pakistan should take and consider are enlisted below:

- Make sure that the brand, formula, and Urdu names of herbs are included into Med Vigilance e-Reporting. If the patient used any herbal, Desi, or Unani products, remind reporters to include this information [31].
- Specific DHI hazard warnings, such as "liquorice + digoxin/diuretics," "ashwagandha + thyroid medications," or "high-volume green tea + warfarin," can be issued by DRAP/PNPC. Dedicated herbal pharmacovigilance streams are supported by WHO guidelines [5].
- Include a required herbal part in medication reconciliation, and teach pharmacists how to check for DHIs in diabetic and anticoagulation clinics.
- Assist community chemists and hakeems/homeopaths with recommendation factors such as palpitations, bleeding, and hypoglycemia.

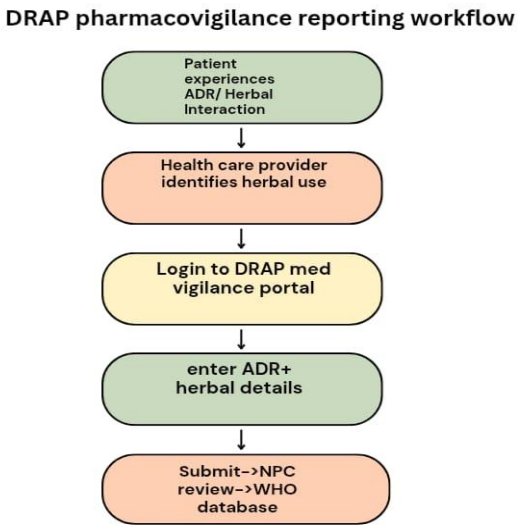

Figure 3: DRAP Pharmacovigilance Reporting Workflow

Research Need and Priorities

- Prospective cohorts measuring the prevalence of DHI in clinics for cardiology and endocrinology.
- Bioanalytical evaluations of the potency and pollutants of locally marketed herbal products.
- PK/PD studies of fenugreek–sulfonylurea and black seed–warfarin.
- Pharmacogenetics that may influence the risk of DHI (CYP2C9/2C19 in Pakistani people).

LIMITATIONS

Due to limited trials, inconsistent preparations, and dependence on case reports, the evidence for many plants is still inconsistent. Due to the paucity of human clinical interaction evidence for a number of regionally popular plants (like ajwain), careful extrapolation from mechanistic/animal studies is required[32].

CONCLUSION

Given high herbal use, polypharmacy, and limited local data, drug–herbal interactions represent a substantial, under-recognized safety risk in Pakistan. Immediate, low-cost steps—routine herbal history-taking, focused clinical warnings, and robust ADR reporting via DRAP—can reduce harm while we generate stronger local evidence.

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