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"PHARMACOVIGILANCE OF *RASAUSHADHI*: A CRITICAL REVIEW OF ADVERSE EVENT REPORTS, SAFETY SIGNALS AND THE REPORTING SYSTEM IN INDIA"

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ABSTRACT

Background: *Rasaushadhi* (herbo-mineral and herbo-metallic formulations) carry particular safety concerns because they intentionally contain metals such as mercury, lead and arsenic. India has had a national pharmacovigilance programme for Ayurveda, Siddha and Unani drugs since 2008, restructured in 2017, yet signals relating to *Rasaushadhi* continue to come mainly from case reports and market surveys. **Objective:** To review the sources of safety information on *Rasaushadhi*, the structure and performance of the pharmacovigilance system for Ayush drugs, and the barriers to effective reporting. **Methods:** A critical narrative review of case reports and case series, market surveys, preclinical and clinical safety studies, surveys of practitioners, and descriptions of the national pharmacovigilance programme. **Results:** The most serious documented harms are metal poisonings, including lead poisoning clusters and chronic arsenic poisoning with blood arsenic of 93–330 µg/L after months to years of use. Market surveys have found heavy metals in every one of 42 over-the-counter products in one Indian study. Practitioner surveys show low reporting: in one, 92% of Ayurveda doctors had heard of pharmacovigilance but only 5% knew how to report an adverse reaction. Clinical trials rarely include metal biomonitoring, and causality assessment tools are not adapted to multi-ingredient formulations. **Conclusion:** Pharmacovigilance of *Rasaushadhi* needs active surveillance with laboratory confirmation, product-level identification, training of practitioners and pharmacists, and integration of metal biomonitoring into clinical studies.

KEYWORDS: Pharmacovigilance; *Rasaushadhi*; Adverse drug reactions; Herbo-mineral formulations; Heavy metals; Ayush; Causality assessment

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INTRODUCTION

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. For herbal and traditional medicines, the World Health Organization has issued guidance on integrating safety monitoring into national pharmacovigilance systems[1]. *Rasaushadhi* pose specific challenges within this framework: they contain metals by design, are often prescribed for long periods, are frequently combined with other formulations, and are sold both on prescription and over the counter.

Classical Ayurveda recognises that medicines can cause harm when they are poorly prepared, wrongly prescribed or used in excess, and it lays down rules for dose, duration and suitability. Modern pharmacovigilance offers tools to detect such harms systematically[2,3]. This review examines what is known about adverse events associated with *Rasaushadhi*, how the reporting system for Ayush drugs is organised, and how it could be strengthened.

METHODS OF THE REVIEW

This is a critical narrative review. Literature was identified through PubMed, PubMed Central, DOAJ, Crossref-indexed records and journal archives, using the terms pharmacovigilance, adverse drug reaction, Ayurveda, Ayush, *Rasaushadhi*, herbo-mineral, heavy metal, lead poisoning, mercury, arsenic and case report. Descriptions of the national programme were taken from published accounts and official documents. Evidence was grouped by source of safety information.

THE PHARMACOVIGILANCE SYSTEM FOR AYUSH DRUGS IN INDIA

A National Pharmacovigilance Programme for Ayurveda, Siddha and Unani drugs was launched in 2008 under the then Department of AYUSH, with a national protocol and a network of regional and peripheral centres[4,5]. Its early progress and challenges were reviewed soon after launch[2,6]. In 2017, the Ministry of AYUSH introduced a central sector scheme for pharmacovigilance of Ayurveda, Siddha, Unani and Homoeopathy drugs, with a national coordination centre, intermediary centres and peripheral centres, and a mandate that included monitoring of misleading advertisements[7]. The need for pharmacovigilance of herbal products in India has been recognised for some time[8], and reporting for herbal products also occurs through the Pharmacovigilance Programme of India, and analysis of its database has documented adverse reactions to herbal products[9,10].

SOURCES OF SAFETY INFORMATION ON RASAUSHADHI

Table 1. Sources of safety information on *Rasaushadhi* and their strengths and limitations

Source	Examples	Strengths	Limitations
Case reports and case series	Lead poisoning series in the USA; chronic arsenic poisoning in India	Establish that serious harm can occur; often include laboratory confirmation	Cannot estimate frequency; product often not analysed or identified
Public health investigations	Lead poisoning cluster with product analysis	Link exposure, product and outcome	Rare; depend on detection of a cluster
Market surveys	Heavy metals in products bought online or over the counter	Show prevalence of metals in products	Do not show clinical harm; methods vary
Preclinical safety studies	Repeated-dose rat studies of compound formulations	Controlled dose and duration	Short duration; single products; animal-to-human extrapolation
Clinical studies	Safety laboratory tests in trials	Human data at therapeutic doses	Small; rarely include metal biomonitoring
Spontaneous reporting	National programmes	Broad coverage	Severe under-reporting; product details often missing

1. Case reports and clusters

The most serious and best-documented harms are metal poisonings. The United States Centers for Disease Control and Prevention reported lead poisoning associated with Ayurvedic medications in five states[11], and a public health investigation of a lead poisoning cluster among consumers of Ayurvedic medicine led to analysis of the preparations involved[12,13]. In India, three patients who had taken Ayurvedic preparations for 4 months to 9 years for skin disease and diabetes developed chronic arsenic poisoning, with blood arsenic of 93–330 µg/L and persistent neuropathy in two[14]. These reports share common features: long-term use, often without supervision; products of uncertain composition; and diagnosis only after typical signs of metal toxicity had developed.

2. Market surveys

Surveys of products provide a complementary signal. About one in five Ayurvedic products bought via the Internet contained detectable lead, mercury or arsenic, with *Rasa Shastra* products more often positive[15]. In a survey of 42 over-the-counter Ayurvedic preparations from licensed shops in Chandigarh, heavy metals were detected in every product, with a median mercury concentration of 13.52 µg/g and a maximum of about 61,096 µg/g[16]. Such surveys cannot show harm, but they identify products that warrant investigation.

3. Preclinical and clinical safety studies

Preclinical studies typically report good tolerance, but with signals that deserve follow-up. In a 120-day rat study of Mahayograj guggulu, a compound formulation containing *bhasmas*, the product contained 25.8 µg/g lead, and serum alkaline phosphatase rose significantly at all doses, with reductions in white cell and lymphocyte counts at one dose; the authors described the product as generally well tolerated[17]. A pilot study has assessed the safety of the arsenical *Rasamanikya* in healthy volunteers[18]. Clinical trials of *Rasaushadhi* rarely report blood or urine metal levels; in one cohort study of an Arogyavardhini Vati regimen, urinary mercury was mentioned but not reported[19].

4. Spontaneous reporting

Spontaneous reporting of adverse reactions to Ayurvedic medicines remains very low. Surveys of practitioners consistently show a gap between awareness and practice. In Wardha, 92% of 38 Ayurveda doctors had heard of pharmacovigilance, but only 37% knew its meaning, 18% had encountered an adverse reaction, 5% knew how to report it and 3% kept a record[20]. Similar gaps have been found among physicians in Himachal Pradesh and among Ayurveda pharmacists[21,22]. Contributing factors include the belief that Ayurvedic medicines are inherently safe, uncertainty about whether an event is drug-related, lack of reporting forms and feedback, and concern about reputational consequences.

SPECIFIC CHALLENGES FOR RASAUSHADHI

1. Product identification

Effective pharmacovigilance needs the exact product: manufacturer, batch and composition. *Rasaushadhi* are often dispensed loose, compounded by practitioners, or bought from multiple sources, and patients may not know what they are taking. Without product identification, reports cannot be linked to a manufacturing problem.

2. Causality assessment

Standard tools such as the Naranjo algorithm assess causality for a single drug[23]. Patients taking *Rasaushadhi* often take several multi-ingredient formulations at once, together with conventional drugs, and metal toxicity develops slowly. Causality assessment therefore needs to include laboratory evidence of exposure (blood or urine metal levels), analysis of the product, and the time course of exposure and recovery after withdrawal. Adapted tools for traditional medicines that incorporate these elements are needed.

3. Cumulative exposure

The same metal may be present in several co-prescribed formulations, and cumulative exposure may exceed what any single product would suggest[3,24]. Prescription audits and product labels that state metal content per dose would allow cumulative exposure to be estimated.

4. Distinguishing intended metals from contamination

A signal from a *Rasaushadhi* may reflect the intended metal, an unintended contaminant, or poor processing that leaves the metal in a more toxic form. Product analysis, ideally including speciation, is needed to distinguish these possibilities and to direct regulatory action to the right point in the supply chain.

RECOMMENDATIONS

Table 2. Recommendations for strengthening pharmacovigilance of *Rasaushadhi*

Area	Recommendation
Reporting	Simple reporting forms and mobile tools for practitioners, pharmacists and patients; feedback to reporters
Training	Pharmacovigilance training in undergraduate and postgraduate Ayurveda curricula and continuing education
Product identification	Batch numbers on all products; labels stating metal content per dose; retention of samples by manufacturers
Laboratory support	Access to blood and urine metal testing and product analysis for suspected cases
Active surveillance	Cohort event monitoring of patients starting selected *Rasaushadhi*, with baseline and follow-up metal levels
Clinical research	Mandatory reporting of metal biomonitoring in clinical trials of *Rasaushadhi*
Causality	Adapted causality assessment for multi-ingredient formulations incorporating exposure biomarkers and product analysis
Market surveillance	Regular testing of over-the-counter products and action on non-compliant manufacturers

RESEARCH GAPS

Key gaps include: the incidence of adverse events with commonly used *Rasaushadhi* in routine practice; blood and urine metal levels in long-term users; validated causality tools for multi-ingredient traditional medicines; and evaluation of interventions to increase reporting among practitioners. Cohort event monitoring in teaching hospitals, where prescriptions and patients can be followed, would be a feasible starting point.

CONCLUSION

The safety signals for *Rasaushadhi* come mainly from case reports of metal poisoning and from market surveys, while spontaneous reporting remains weak and clinical studies rarely measure metal exposure. India has the structure of a pharmacovigilance system for Ayush drugs, but its effectiveness for *Rasaushadhi* depends on product identification, practitioner training, laboratory support and active surveillance. Strengthening these elements would protect patients and also provide the evidence needed to defend well-made formulations against blanket criticism.

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