

# Pharmacovigilance: A need in ayurvedic medicine system

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## Abstract

The core principle of the pharmaceutical trade is to establish product safety and effectiveness through clinical trials. The approval procedures govern by the U.S. Food and Drug Administration and clinical trial methods, however, will give a guarantee of safety from all variety of medicine under all circumstances. Despite this truth, is a procedure pharmaceutical corporations and physicians will implement to support pharmacovigilance. Once designed the existing analysis and development practices will enhance patient safety, whereas reducing or perhaps stopping pricey safety connected withdrawals. In 1961, after detection of teratogenic disaster, the World Health Organization (WHO) started its International Drug Monitoring program. The more international demand of Ayurveda forced the regulators to implement a constant program for Ayurveda. So that some doctors, scientists, and public will report the adverse drug reactions when using Ayurvedic/herbal formulations. The WHO so convinced the Department of AYUSH, Ministry of Health and Family Welfare, Government of India, to start the same program for Ayurveda, as a way to making sure the protection and efficaciousness of Ayurvedic medicines. Ayurveda as a proper medical system, which is recognized by Government of India, initiated the institutionalized coaching a century ago. Now, India has 196 undergraduate schools and 55 postgraduate centers.

**Key words:** Adverse drug reaction, awareness, Ayurvedic medicine, pharmacovigilance, safety, U.S. Food and Drug Administration, World Health Organization

## INTRODUCTION

The “World Health Organization (WHO) defines the pharmacovigilance (PV), as the pharmacological science relating to the detection, evaluation, understanding, and prevention of adverse effects, particularly long-term and short-term side effects of medicines”.<sup>[1,2]</sup> In general, to ensure efficacy and safety, the drug needs to pass through various clinical trials before utilization.

Complete drug safety includes every domain of safety, for example, comparison standards, and techniques of measurement. The safety of marketed drugs put forward for medical use in huge populations is necessary, and the technique related to this is known as PV.<sup>[3]</sup> PV in India was started back in 1986 when 12 regional centers were proposed. No activities were noted down for about a decade during this project. After this, India then joined the Uppsala, Sweden-based WHO-adverse drug reaction (ADR) monitoring program in 1987. In beginning for

ADR monitoring in the country, 8 regional centers were set up in Varanasi, Thiruvananthapuram, Guwahati, Jaipur, Bhopal, New Delhi, Bengaluru, and Chennai.<sup>[4]</sup> The PV centers in India are shown in Figure 1.

The responsibility to monitor the adverse drug reaction of marketed medicine was assigned to three centers - Jawaharlal Nehru Hospital, Aligarh, All India Institute of Medical Sciences, New Delhi, and King Edward Memorial Hospital, Mumbai. They had to submit the report to the Drug Regulatory Authority of India. However, this too did not yield much. Finally, in the year 2005, the National Pharmacovigilance Program (NPP) was launched

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**Received:** 03-05-2017

**Revised:** 07-09-2017

**Accepted:** 11-11-2017

which was sponsored by the WHO and it was funded by the World Bank, which was supervised by the National Pharmacovigilance Advisory Committee.<sup>[5]</sup> However, this program was suspended due to the end of the World Bank funding in mid-2009. As there is a need of improved ADR monitoring required in India, in 2010, under the sponsorship of Health Ministry, a nation-wide revised ADR monitoring program “PV Program of India ” was launched.<sup>[6]</sup> Under this program, ADRs are spontaneously reported by the doctors/scientist of adverse drug reaction monitoring centers (AMC). These 179 AMCs are set up in medical colleges approved by the Medical Council of India across India.<sup>[7]</sup> These AMCs are collecting adverse event data as per Standard Operating Procedure, regularly taking follow-up if needed and uploading these reports in Vigiflow (net-based software used for ADR reporting).<sup>[8]</sup> These Individual Case Safety Reports are then reported to the National Coordination Center for evaluating the causality assessments of ADRs performed using the WHO-UMC causality assessment system [Figure 2].

The purpose of this program is to collect, collate, and analyze this reported data to arrive at an inference to recommend regulatory interventions for safeguarding the health of Indian population by ensuring that benefit outweighs the risks associated with the use of medicines.

## PV IN AYURVEDA

PV is defined as “the detection, assessment, understanding, and prevention of adverse effects of drugs or any other possible drug-related problems”.<sup>[10]</sup>

The technical term “PV” does not exist in Ayurvedic texts but the spirit of PV is available throughout Ayurveda’s classical literature; for example, in the Charaka Samhita, it describes all type of adverse reactions related to medicines.

The major responsibility of PV is to improve medical health and safety of the patient during therapy and medical care and thus actively encourages the rational use of medications.<sup>[11]</sup> Due to this basic ideology of Ayurveda, it gives rise to the common trust that the Ayurvedic medicines are safe.

The Ayurvedic literature, the Charaka Samhita, has evidences related to drug-drug and drug-diet incompatibilities when synergistic medicines are prepared or used without considering incompatibilities. Hence, these factors along with “*Anupan*” therapeutic method and “*Shodhan*” pharmaceuticals principles prevent the onset of many unfortunate reactions. Prevention of this kind is a major goal of PV programs.<sup>[12]</sup>

There are two categories of “Ayurvedic” medicines, which are available in the market: First, which are as per descriptions in Ayurveda Samhitas called classical Ayurvedic formulations,

and second, patent and proprietary formulations made from the extracts of herbs.<sup>[13]</sup>

The ADR is harmful and inadvertent responses of a marketed drug, which is related to dose for diagnosing, treating, or modifying the organ function.<sup>[14]</sup> The modern medicines are evolved from natural sources such as plants, microorganisms, and animals, of them the majority of the modern medicines are directly or indirectly of plant origin.

The types of adverse reactions are established first for modern medicine and the same can be applied equally to herbal medicine. ADRs are classified as follows:

Type A (acute/augmented): It is dose dependent and explained by pharmacology of the drug.

Type B (bizarre/idiosyncratic): It is not dose dependent or expected by pharmacology.

Type C (chronic/cumulative): It generally gives cumulative effect.

Type D (delayed/onset): It is carcinogenic and genotoxic.<sup>[15]</sup>

As reported by Reginster and Heinrich that Aristolochia has shown chronic toxicity (Type C). The most common reported

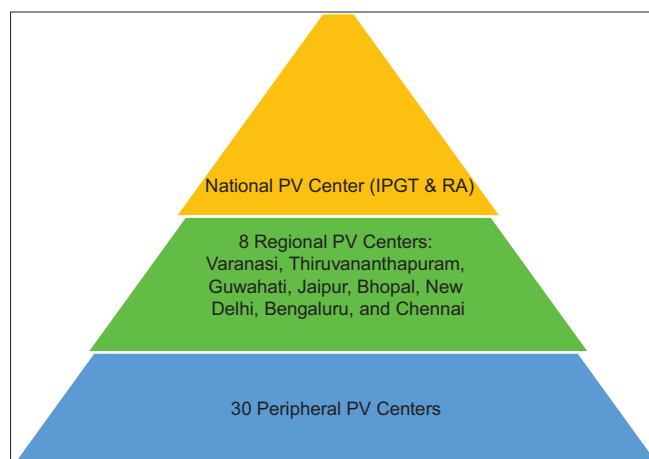


Figure 1: Pharmacovigilance centers in India

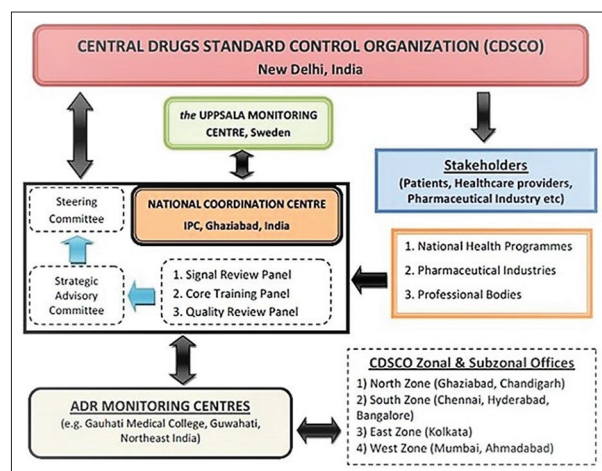


Figure 2: Program communication and flow of adverse drug reaction reports<sup>[9]</sup>

adverse effects by Ayurvedic and herbal drugs are hepatic and renal in origin.

The Ayurvedic/herbal medicines often contain multiple ingredients, so it is quite difficult to identify the exact causative element associated with the ADRs. A list of known ADRs associated with herbal drugs are shown in Table 1.

Herbal drug-associated adverse drug reactions (ADRs) are also reported and are mentioned in Table 2.

## DETECTION OF ADVERSE REACTIONS TO AYURVEDIC MEDICINES

An adverse reaction (ADR), “A noxious and unintended response to a marketed health product, which occurs at doses normally used or tested for the diagnosis, treatment, or prevention of a disease or the modification of an organic function.”<sup>[20]</sup> There is a common misbelief about the Ayurvedic medicines that they are deprived of harmful effects and reactions. Perhaps, this illusion is due to the solid

belief among medical practitioner and prescribers. It is the major challenge to detect the adverse reactions to Ayurvedic medicines. To know the exact reason, the way has a lot of hurdles, including:

- The terminology of adverse drug reaction monitoring is not covered in the Ayurvedic literature.
- Methods for drugs safety have not developed gradually and up to an acceptable extent in Ayurveda.
- Because information on medicines available in the ancient literature of Ayurveda is not easily accessible.
- To detect path is a tough task due to strong belief about the safety of these medications leading to a lack of reporting and collection of data related to any preparation or formulation.
- The patients also use the medicines from different systems of medicine and lead to find the actual cause.
- The deficiency in quality inspection, control, and assurance in processing the Ayurvedic formulations may be a leading factor in diagnosing the adverse reaction.<sup>[21]</sup>

The NPP has given support to report all suspected drug-related adverse effects including all type of herbal and alternative

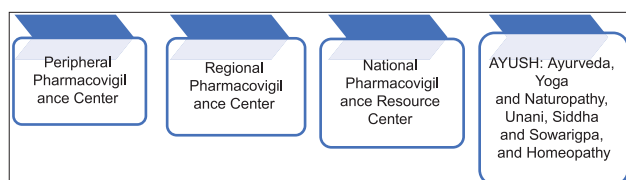
**Table 1: List of herbs with suspected or known adverse effects<sup>[16]</sup>**

Herbal drug	Adverse effects
Ginkgo biloba	Bleeding
St. John's Wort	Gastrointestinal disturbances, allergic, reactions, fatigue, dizziness, confusion, dry mouth, photosensitivity
Ephedra (Ma Huang)	Hypertension, insomnia, arrhythmia, nervousness, tremor, headache, seizure, cerebrovascular event, myocardial infarction, kidney stones
Kava ( <i>P. methysticum</i> )	Sedation, oral and lingual dyskinesia, torticollis, oculogyric crisis, exacerbation of Parkinson's disease, painful twisting movements of the trunk, rash
<i>Aristolochia</i> sp. (found use in Chinese medicine)	Kidney toxicity, carcinogenicity
Kalmegh ( <i>A. paniculata</i> )	Urticaria <sup>[17]</sup>
Chamomile ( <i>C. recutita</i> )	Asteraceae dermatitis
Coneflower ( <i>Echinacea</i> spp)	Asteraceae dermatitis and anaphylaxis
Thyme ( <i>T. vulgaris</i> )	Contact dermatitis with topical use of the oil

*P. methysticum*: *Piper methysticum*, *T. vulgaris*: *Thymus vulgaris*, *C. recutita*: *Chamomilla recutita*, *A. paniculata*: *Andrographis paniculata*

**Table 2: List of specific herbal drugs and their adverse interactions<sup>[16]</sup>**

Herb	Drug	Adverse effect
Ginkgo biloba	Drugs such as aspirin, warfarin, ticlopidine, clopidogrel, dipyridamole, garlic, Vitamin E	With aspirin - retards aspirin, absorption
Psyllium seed	Coumarin derivatives	Retards absorption of drug
Ephedra	Caffeine, decongestants, stimulants	Maybe additive in nature
Feverfew	Aspirin	Additive effects
Echinacea	Aspirin, rosuvastatin, escitalopram, atorvastatin, esomeprazole, montelukast, levothyroxine, alprazolam, cetirizine	Toxic side effects <sup>[18]</sup>
Devil's Claw (Harpagophytum)	Warfarin	Addictive effects <sup>[19]</sup>



**Figure 3:** Flowchart showing the flow of pharmacovigilance reports

medicines. However, the total reportings related to herbal drugs have been appallingly low. The general process of flow of PV is shown in Figure 3.<sup>[22]</sup>

## WHO CAN REPORT AT PV CENTER?<sup>[1,23,24]</sup>

A medical practitioner

Scientist/Pharmacists

A qualified person from Pharma Industry (Regulatory manager)

Products under investigation (clinical trials)

The patient itself can report the side effects

## WHAT TO REPORT?<sup>[1,24,25]</sup>

All types of adverse reactions which may lead to

- Death of a patient
- Risk to life
- Admitted to hospital at initial or for prolonged time
- May cause disability (significant, persistent, or permanent)
- Congenital anomaly
- Resistance.
- Drug interactions.

ADRs associated with radiology contrast media, vaccines, diagnostics, drugs used in traditional medicine, herbal remedies, cosmetics, medical devices, and equipment.

## WHAT HAPPENS TO THE SUBMITTED INFORMATION?<sup>[1,25,26]</sup>

The submitted report kept confidentially and patient's identity is not mentioned on the form, and the patient's identifier is mentioned only. This report is forwarded to respective Regional PV Centers by Peripheral PV Centers. The causality analysis will be done by these respective Regional PV Centers and after that this information will be passed to the NPRC (National Pharmacovigilance Resource Center). The NPRC analyzed this data statistically and submitted to the Department of AYUSH, Government of India.

## Recommendations

Using different ways, we can enforce PV systems to herbal and Ayurveda:

- The concept of PV should be incorporated into the curriculum at the undergraduate and postgraduate level.
- Encourage studies on drug safety.
- ADR reporting to regulators should be mandatory.
- Create awareness about the science of PV among physicians, patients, and paramedical staff.
- Development and validation of scales to assess the causality of the reported reactions to herbal and Ayurvedic medicines.
- There is a strong need to train the experts in the pharmacovigilance field. So, that he can not only report but also helps to evaluate the adverse reactions

## CONCLUSION

All drugs available in the world are capable of producing good and bad effects. To minimize the bad effects, the drugs are supposed to be used judiciously. Medicinal herbs attained a significant role in curing the human welfare not only in the diseased condition but also to maintain the proper health.<sup>[27,28]</sup>

The need of this study is to generate awareness to the pharmaceutical companies and physicians and motivated them to find causes and to report any adverse effects observed by them during the process (preparation or treatment). Because authentic drugs are essential for effective therapy.<sup>[29,30]</sup>

- Need of development and standardization of Ayurvedic drugs.
- Regulatory aspects of Ayurvedic drugs.

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**Source of Support:** Nil. **Conflict of Interest:** None declared.