Review Article

Current Status of Pharmacovigilance in Herbal and Traditional Medicines: A Review.

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ABSTRACT

Pharmacovigilance is the study of the safety of pharmaceutical medicines to monitor and detect adverse drug reactions, which may be unrecognized during clinical trials. Traditional medicines often use herbal components, and some of them can cause severe adverse effects. Yet the safety of herbal or traditional medicines is unknown, even though they are believed to be safe. This area of pharmacovigilance is still in an immature stage, although there are multiple herb-drug interactions, herb-herb interactions, and certain herbal products are contraindicated in some conditions. The pharmacovigilance of herbal medicines is still in its immature stage, although the World Health Organization (WHO), the US Food and Drug Administration (FDA), and various agencies in different countries have established reporting systems for adverse drug reactions. But most of the cases go unreported. This review presents the status of herbal pharmacovigilance and highlights the importance of implementing pharmacovigilance procedures for polyherbal medications, promoting rational use and appropriate treatment methods.

Key words: Pharmacovigilance, Herbal Medicine, Drug-Related Side Effects and Adverse Reactions, Herb-Drug Interactions

Pharmacovigilance is the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities [1]. The objective of this is to extend safety monitoring and detect drug adverse events that are unrecognized despite evaluation in clinical trials. Although pharmacovigilance was developed to monitor pharmaceutical medicines, it is also used for the evaluation of the safety of other medicinal products, including herbals, vaccines, and medical devices [2].

Pharmacovigilance monitors and acts in case of adverse reactions related to drugs or medicines in the market. There are many communication facilities where we can report the benefits and harmful effects of the treatments given by health practitioners and some portals where reporting of the side effects or adverse reactions of drugs can be made. The World Health Organization (WHO), the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) have developed pharmacovigilance laws. The FDA introduced a national electronic system named "Sentinel Initiative" in May 2008 to monitor the safety of FDA-regulated products, including pharmaceuticals, biopharmaceuticals, vaccines, and healthcare products [3, 4].

The safety of Herbal products is still a mystery, although it is believed that they are safe. Herbal products are made from various plants and include hundreds of natural compounds.

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The chemical composition and action of many of these compounds are unknown. This review looks at the current scenario of pharmacovigilance for herbal products and components in the world and how well they are established. It also highlights the importance of maintaining the safety of herbal medicines in practice.

The traditional systems of Medicine

The traditional system of medicine (TSM) in India includes Ayurveda, Siddha, Homeopathy, Unani, Yoga, and Naturopathy [5]. Ayurveda has been practiced worldwide. Herbs are commonly used in Ayurveda. These medicines are effective and offer a lifestyle change. Many allopathic medications like ephedrine, paclitaxel, artemisinin, and aspirin are derived from herbs. But there is little preclinical proof to support the safety and effectiveness of most of these herbal products [6].

In China, Traditional Chinese Medicine (TCM) is the traditional way of treatment to cure various diseases, including cancer. Here, many natural products or their components work on the principle of imbalances of two opposing energy forces, Ying and Yang. In 1989, a pharmacovigilance cell for the adverse drug reaction monitoring system was established for both TCM and allopathic medicines. After it was established, approximately 10-15% of TCM users reported adverse reactions. This model is still in its immature stage,

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which requires understanding every aspect of the drugs, their origin, processing, packaging, storage, and intake during treatment. A network called HERB (High-Throughput Experiment and Reference-Guided Database with TCM) was established in China to assess the effect of herbal medicines [7].

Traditional Japanese herbal (Kampo) medicines are used to treat many disorders in Japan. In 1990, a Kampo formula Shosaikoto, which is derived from the root of Bupleurum falcatum was found to cause interstitial pneumonia and deaths. After this incident, a Japanese Adverse Drug Event Report database (JADER database) is maintained by the Pharmaceutical and Medical Devices Agencies (PMDA) for collecting the ADR reports in medicines, including Kampo medicines [8].

In low-income countries like Africa, the challenges faced during pharmacovigilance are the use of many local languages; hence, translating the reports of adverse reactions to the public is difficult. Administration of drugs for the public is also difficult in these countries due to negligence and a poor information system [9].

In the US, where herbal medicines and natural products are supplied as dietary supplements, health professionals and consumers can report adverse reactions to the FDA MedWatch scheme [10].

In the UK, the spontaneous reporting system referred to as the 'yellow card' scheme is available for the same purpose. Australia has blue cards for this. In the UK, the yellow card was modified for the inclusion of herbals in 2000. However, regarding the accurate ingredient lists, botanical naming of the medicinal herbs, processing, and product quality, there are still controversies. In the UK, the Medicines and Healthcare Products Regulatory Agency receives approximately 20,000 yellow card reports per year, but this figure includes only around 100 herbal products. Efforts to improve reporting by extending it to nurses, pharmacists, and consumers were made. Yet, there was no significant increase in the reporting. Sweden and Italy have carried out studies on herbal ADRs in 2008 and 2009 by Menniti-Ippolito et al. and Jacobsson et al., respectively [10].

The process of pharmacovigilance of traditional medicines is shown in Figure 1. The reporting agencies vary from country to country, and the form also varies accordingly. Both the patients and the clinicians should report to the centres.

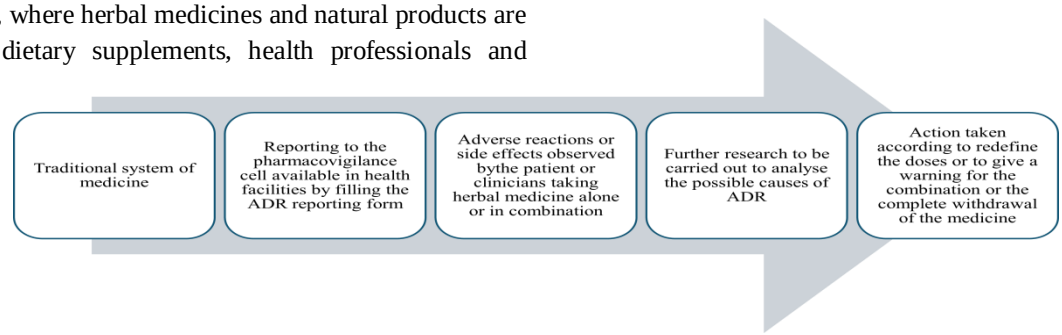


Figure 1. Process of pharmacovigilance of herbal medicines (herb-vigilance) [11].

Herbal Medicines Reactions

Pharmacovigilance of herbal medicine is a part of the pharmacovigilance of medicines. The unintended reactions of herbal medicines may be caused by.

1. Side effects, which are detectable by pharmacodynamics and often predictable
2. Overdose, tolerance, dependence, and intoxication
3. Allergic reactions
4. Long-term toxic effects: renal, cardiac, liver, and neurotoxicity.
5. Interactions between herbal remedies and prescription drugs regarding pharmacodynamics and pharmacokinetics. These interactions may be serious and sometimes even fatal [12] (Table 2).

Table 1. Adverse reactions of the excess consumption of herbal drugs [12]

Name of the compound	Plant source	Dose required	Adverse reaction
Ephedrine	Ephedra vulgaris	5-10 mg IV bolus (Akovaz, Corphedra, Emerphed, generics) 4.7-9.4 mg IV bolus (Rezipres)	Nervousness, anxiety, dizziness, headache, loss of appetite, tachycardia, sweating, vomiting, chest pain, and arrhythmia in severe cases [13].
Ginkgo	Ginkgo biloba	60 mg to 240 mg	Interaction with other drugs like Efavirenz (HIV treatment), Ibuprofen [14].
Taxol	Taxus brevifolia	60 mg per square meter of body surface area, 4 mg per kg body weight	Gastrointestinal, hematological, musculoskeletal, dermatological, and neurological effects [15].
Aspirin	Salixsp.	325 to 650 mg four times a day	Interact with NSAIDs and blood thinners [16].
Aloe vera	Aloe vera	50-200 mg daily (capsule of gel)	Carcinogenic, genotoxic, hepatotoxic, haemorrhagic, Purgative effects, male infertility, and nephrotoxic effects [17].

Even though many herbal medications show promising efficacy, very little is known about the possible side effects. Many of them are not evaluated or are not being taken under supervision. Low quality, improper processing techniques, and supply of inferior/misbranded/adulterated herbal drugs can result in toxicity.

Recent laboratory analyses confirm that herbal medicines are often mixed with allopathic components to increase their efficiency [18]. Numerous contaminations of herbal medications have been discovered in recent studies. Metals, microorganisms, mycotoxins, pesticides, and leftover solvents are identified in herbal medicinal products [19].

In India, National regulatory agencies and National safety monitoring or pharmacovigilance centers normally do not exchange information on national regulations on herbal medicines. Quality assurance and control procedures, like national quality requirements and standards for herbal ingredients, good manufacturing practices (GMP) for herbal medicines, labelling, and licensing schemes for manufacture, importing, and marketing should be established in any country that governs herbal medications. For the safety assessment of herbal medicines, pharmacovigilance must be employed [20].

Challenges of herbal pharmacovigilance

Herbal medicines in Europe came from Chinese, Indian, North and South American, and African systems, as well as from European systems. This diversity causes difficulty in the herbal pharmacovigilance to identify the herb names, including the botanical, common, pharmaceutical name, or herbal drug names, and validation of the botanical identity of the herbal ingredients [2].

Uppsala Monitoring Centre (UMC) was established, which takes ADR reports from more than 100 countries, and in 2010, its database had over 4 million reports, where around 21,000 herbal or natural products were included [21]. These are incorporated in a single database and reviewed by experts in this field to detect the suspected signals.

Table 2. Factors influencing the qualitative and quantitative chemical profile of herbal products.

S No.	Factors	Types
1	Geographical origin	Climate, soil, photoperiod
2	Genotype	
3	Parts of the plant	Leaves, stems, roots, and root bark
4	Harvesting time	Year, season, time of day, and conditions
5	Storage, processing, extraction	
6	• Combinations of herbs • Processing of the combined herbs as medicines	

Unlike synthetic medicines, herbal medicines are typically chemically complex products and cannot be isolated into single compounds. The factors influencing the qualitative and quantitative chemical profile are shown in Table 2 [2].

Identifying adverse reactions

The classification of adverse reactions in herbal medicine is shown in Table 3.

Table 3. Adverse reactions of Herbal Medicine [2]

Type A	Acute/Augmented	Dose-related and explained by the pharmacology of herbs
Type B	Bizarre/Idiosyncratic	Not dose-related or predictable by pharmacology
Type C	Chronic/Cumulative	Cumulative Effect
Type D	Delayed Onset	Carcinogenic, Genotoxic

Herb-drug interactions (HDIs)

HDIs occur when the active components of herbal medicines alter the pharmacokinetics or pharmacodynamics of conventional medications, causing therapeutic failures, increased toxicity, or adverse effects. Herbal supplements are often used with prescription drugs. More than one-third of US adults take herbal supplements. Higher levels of education and advanced age are connected to higher use of herbal medicines. Since herbal products are from natural sources, people believe them to be always safe. It is proven that there are many adverse effects when prescription drugs and herbal supplements are taken together. When herbs like garlic, ginkgo, etc., are taken with warfarin, an anticoagulant, bleeding will become severe.

To monitor and evaluate these interactions, effective pharmacovigilance techniques need to be established. The challenges faced by agencies in establishing worldwide regulations include variability in herbal composition, lack of standardized testing, and limited clinical trials. FDA (USA), EMA (Europe), MHRA (UK), and WHO are some of the Several regulatory bodies that have established guidelines for assessing and managing HDIs [22]. Figure 2. Shows the pathway and effects of herb-drug interactions.

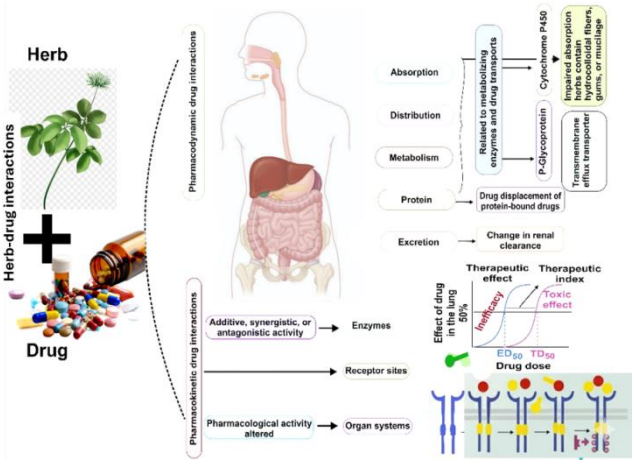


Figure 2. Pharmacokinetic and pharmacodynamic effects of herb-drug interactions [23].

Herb-Herb Interaction

When preparing multiple co-prescriptions, herb-herb interaction can occur. Although each herb in a prescription is suggested for a specific symptom, the combination becomes a random collection of herbs. For the past, herb-herb combinations have been used in treatments. While the pharmacological processes are unknown, they are likely to cause pharmacokinetic, pharmacodynamic, and/ or polyvalent effects [24].

Other Herbal Interactions

Many herbs and herbal components interact with food or medications, which can sometimes lead to adverse outcomes. Some plant products are contraindicated for some patients. Some of the herb interactions are depicted in Table 4.

Table 4: Common interactions of herbal drugs along with examples [25].

S no.	Common types of interaction of natural drugs	Examples
1	Herb-herb interaction	Piper betel with Garcinia Morella Basella alba with Sesamum indicum Glycyrrhiza roots with Euphorbia pokinensis root Aconite with Bletilla Striata rhizome Liquorice with Seaweed
2	Herb-food interaction	Radish and Milk Equal quantity of Madhu and Grutha. Sesame Seeds and Black cumin. Shilajatu and Kakmachi. Asafoetida and Honey. Garlic and Milk. Kampillaka and Buttermilk. Bhallataka and Hot Water. Kakmachi and Honey Boswellia with some foodstuffs.
3	Herb animal origin drug interaction	Meat of Pigeon and Brassica alba Pork and Oil of Coccus nucifera Honey and Ghee
4	Drug disease interaction	Terminalia chebula and Papaya are contraindicated in pregnancy. Tweak and Aloe vera interfere with antidiabetic drugs Ashwagandha may affect digoxin and interfere with thyroid hormone. Ephedrine may interact with steroids
5	Miscellaneous	Idiosyncrasy Drug-activity (exercise) Interaction

Indian regulatory perspectives

In India, the Drugs and Cosmetics Act of 1940 and its amendments govern the regulation of herbal medicines and the assessment of HDIs. The Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homoeopathy) and the Central Drugs Standard Control Organisation (CDSCO) are the other regulatory bodies that also control these aspects.

All-India Institute of Ayurveda in New Delhi has been established as the national pharmacovigilance center, and five AYUSH National Institutes as intermediary pharmacovigilance centers, and 42 AYUSH institutions with clinical facilities as peripheral pharmacovigilance centers. The central drug standard control organization serves as the country's national drug regulatory body, and the Indian Pharmacopoeia Commission, as the country's WHO collaborating center for pharmacovigilance [25].

Future directions

The increasing global use of herbal medicines with conventional pharmaceuticals necessitates a proper pharmacovigilance system to monitor and assess HDIs. Future research should focus on integrating herbal pharmacovigilance into drug safety surveillance by developing standardized reporting systems, improving healthcare professional awareness, and upgrading advanced technologies like artificial intelligence (AI) and big data analytics. Establishing dedicated herbal pharmacovigilance centres within existing drug monitoring frameworks will ensure systematic data collection on HDI-related adverse events.

Regulatory Framework

1. **Drugs and Cosmetics Act of 1940**: This act provides the legal framework for the regulation of drugs and cosmetics in India, including herbal medicines. It divides herbal products under Ayurvedic, Siddha, and Unani drugs and mandates adherence to specified standards. However, presently, the actions have a limited focus on HDIs.
2. **Schedule T:** This is a part of the Drugs and Cosmetics Act. Schedule T outlines Good Manufacturing Practices (GMP) for Ayurvedic, Siddha, and Unani medicines. It regulates quality control but does not currently address HDIs [22].

The WHO urges member nations to enhance national polyherbal medicine legislation, registration, quality assurance, and management to lower these occurrences. It also places a strong emphasis on consumer education and appropriate distribution practices. In addition, when it comes to the distribution of polyherbal medicines, national healthcare authorities ought to emphasize consumer education and qualified practice more. The WHO has praised drug regulatory agencies and national pharmacovigilance centers for their active involvement in the formulation of these recommendations [26].

CONCLUSION

The herbal or traditional system of medicines, despite its widespread use, is often associated with many adverse reactions and even fatal side effects, which go unchecked. Pharmacovigilance with respect to herbal medicines and products is still in its immature stage and hence must be strengthened by proper regulatory frameworks and reporting systems.

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