WWW.IJRPR.COM

**International Journal of Research Publication and Reviews**

Journal homepage: www.ijrpr.com ISSN 2582-7421

# Necessity of Pharmacovigillance Study for Herbal Medicines

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A B S T R A C T

Safe and effective medicine is always a fundamental principle in the provision of any health-care treatment and procedures. Truth of wide use of herbal medicine in the world, maintaining safety of herbal medicines becomes important and a prior area of work. For studying the safety of herbal medicines, pharmacovigillance plays a vital role. Pharmacovigillance (PV) is the science and activities related to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Adverse reactions, medication error, case reports of acute and chronic poisoning (toxicity) Abuse and misuse of medicines, adverse interactions of medicines with chemicals, other medicines and food should be studied in pharmacovigillance for every herbal medicine. Herbal medicine products are widely used nowadays to avoid the synthetic one but these products are not always "safe", particularly when used in combination with other medicines, and result in negative health consequences. To avoid these problems, pharmacovigillance study for every herbal medicine should be done.

**Keywords:** Understanding necessity of pharmacovigillance, herbal medicines safety, public health, safe medicine to people

## 1. Introduction

Pharmacovigillance is most essential for development of reliable information on the safe use of herbal medicines as used in all over world. The current systems were developed for synthetic medicaments and require some modification to address the unique differences of medicinal herbs. Herbal medicine from many different cultures and ethanopharmacological studies are used in every country which adds to the complexities and difficulties of even basic questions such as herb naming systems and chemical variability. Studying to this also is the perception that a 'natural' or herbal product must be safe simply because it is not synthetic which means that the safety element of monitoring for such medicines can be overlooked because of the tag associated with such products. Systematic pharmacovigillance is essential to build up reliable information on the safety of herbal medicines for the development of appropriate guidelines for safe and effective use.

### *1.1. methodology*

- understanding pharmacovigilliance
- need of pharmacovigilliance in improving herbal medicines
- challenging aspects in pharmacovigilliance study of herbal medicines

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- **Understanding pharmaco vigillance:-**

It can be understood as it is the beating heart of pharmaceutical production. Instead of it, there will be no way for assessing the effectivity of drugs in comparison to their side effects. Pharmacovigillance is designed to protect patients and enable the dissemination of knowledge amongst professionals to reduce the risk of Pharmacovigillance is the science and activities including detection, assessment, understanding and prevention of adverse effects or any other drug-related issues. Pharmacovigillance is all about drug regulations and is based on collaborative ties, coordination, communications, and public relations. To develop, manufacture and commercially utilize the drug, a company must adhere to strict rules and regulations. Many of these regulations will aim to the patient's safety and the additional benefit to the patient derived from the drug. This is the mission of drug safety and bold to the discipline play such a central and important role within pharmaceuticals.

An adverse event is a negative activity occurred by administering a drug, most commonly known as a side effect. This can include any unexpected or unwanted symptoms experienced by the patient, including temporary reactions and those previously not associated Pharmacovigillance is the science and activities related to detect, assess, understand and prevent to adverse effects or any other drug-related issues.

A serious adverse event is a reactivity that causes dangerous harm to the individual, resulting in hospitalization, significant disability or incapacitation, congenital abnormality, or at worst, death. Anything that requires interface to prevent these is also classified as serious. In any case, adverse event reporting is the compulsory criteria and critical to the success of Pharmacovigillance.

- **Need of pharmacovigillance in improving herbal medicine:-**

1. The accurate scientific name of the plant, the part used and the name of the manufacturer should be included in the ADR report on herbal medicines.
   Regular training programmes for strengthening national capacity in monitoring the safety of traditional medicine products and for
2. Proactive pharmacovigillance through the promoting awareness should be encouraged.
3. It would be better to start prior with the professional training of health-care students to make a culture of reporting ADRs.
4. National quality specification and standard Networking should entirely manage health facilities (traditional medicine practitioners), manufacturer, drug store (pharmacists) and consumer, harmonize regulations for herbal medicine.
5. Product's life cycle is the perfect way forward and the future direction for drug safety. For instance, the regulatory system should have a technique to collect safety data before marketing approval and after marketing.
6. TRM practitioners should be involved in causality assessment process and they should be trained on the causality assessment.
7. PV should be integrated into curriculum of medical education and should be integrated into good pharmacy practices (GPP) in community pharmacy.
8. Use of latest technology and its development through IT facilities and mobile applications should be encouraged and enhanced.
9. for herbs (selection, sampling, testing of plant material, stability studies), GMP, labelling, and licensing patterns for manufacturing, imports and marketing should be mandatory.

**Challenging aspects in the pharmacovigillance study of herbal medicines:-**

**(1) Insufficient clinical trial data:** Unlike conventional medicines, systematic clinical trial data for many herbal and traditional medicine products is not always available. A license may be issued based on the history of medicinal use. It is not easy to obtain safety and efficacy data on the herbal product.

**(2) Chemical complexity**: Herbal and traditional medicine remedies and products are chemically high complex mixtures comprising several hundreds of constituents. The effects are same as attributed to a group of related constituents rather than a single constituent.

**(3) Non-uniformity (products not standardized):** The profile of constituents is often not uniform throughout a plant and certain parts of the plant can be toxic. The precise profile of constituents is similar to show variation between different batches of herbal materials, and factors such as environment, time of harvesting, storage, processing and drying can affect their variability. This makes it difficult to determine pharmacokinetics, pharmacodynamics and toxicology, and to establish which ingredient causes a safety concern.

**(4) Quality assurance and control:** Unlike herbal pharmaceutical products, herbal and traditional medicines are prepared from materials of herbal origin which are often obtained from various geographical and commercial sources, resulting in uncertain condition. Furthermore, procedures and techniques used in its manufacturing and quality control measure are often very different from those used for herbal medicines.

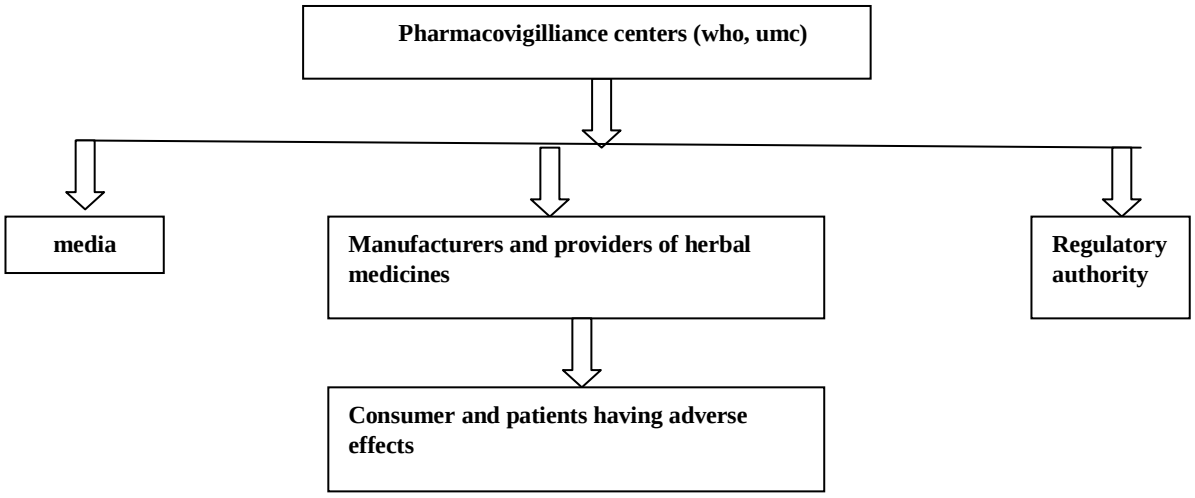
**(5) Lack of technical persons:** facilities and manpower to analyze the problem, particularly in identifying substandard, adulterated and contaminated, wrong medicinal plants, which is a common problem with herbal medicine products.

**(6) Possible interaction** between variety of herbal medicine products and with allopathic medicines and foods.

Variance in product regulation on categorizations of herbal/traditional medicine. For instance, a herbal pro duct in one country can be classified as a dietary/food supplement in another without any health claim.

Insufficient information and lack of access to reliable information support such as product name, part use, etc., for analyzing the products concerned.

***1.2. Communication route of pharmacovigilliance for herbal medicines***




***1.3. Ways of improving pharmacovigilliance in herbal medicines***

There are several prospects in which we can move forward in attempting to improve pharmacovigillance in herbals.

1. Introduce pharmacovigillance concepts into the curriculum of herbals at the undergraduate and postgraduate level.
2. Preparing report of adverse reactions and submitting to regulatory is mandatory for herbal formulations.
3. Human resource development is a main objective for the success of this enterprise. It will be necessary to train herbal experts in the science of pharmacovigillance and include them not only in reporting but also in assessment of the adverse reactions.
4. Healthcare practitioners should remain keen-eyed for potential interactions between herbals and prescription medications, especially when it involves medications with narrow therapeutic indices. Due to the broad use and very easiest availability of herbal medicines, herbal toxicity has become a major issue of concern.
5. The safety and quality of herbal medicine should be ensured through greater research, pharmacovigillance, greater regulatory control, and better communication between patients and health professionals. The recommended approach is to include herbal medicines in existing national pharmacovigillance systems or, where such systems have not yet been developed, to establish comprehensive national pharmacovigillance systems which incorporate coverage of herbal medicines. Pharmacovigillance study of herbal medicine in India is perhaps an unthought of concept as yet; we do not need "Herbal thalidomide" to wake the pharmacovigillance community to the need of the time**.**

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***1.4. Methods of monitoring adverse effect in pharmacovigilliance***

***Spontaneous reporting:***

**S**afety of medicines is commonly monitored through spontaneous reporting systems. There are differences between countries but the principles are the same. Standardized forms are used for reporting of suspected adverse reactions to the regulatory authorities by medical health professionals including physicians, pharmacists, nurses and in some countries, by consumers. The reports are of 'suspected' adverse effects, and a reporter doesn't have to assure the link between drug and effect. Such causality is examined on a case-by-case basis by the reporting centre. Statistical methods are used to find out disproportionate reporting rates which can lead to a safety signal. A 'signal' that shows an adverse effect of interest and one that requires further evaluation and investigation – the link to the drug or herb is not confirmed. Spontaneous reports are merely same to be effective where materials are regulated as medicines and also where products are supplied by health professionals.

In the US where herbal medicaments/naturally derived products are provided as dietary supplements, health professionals and consumers can report suspected adverse reactions to the FDA MedWatch scheme. In the UK the spontaneous reporting system is studied to as the 'yellow card' scheme; other countries like Australia have blue cards. In the UK, the yellow card was changed to allow for the inclusion of herbs in 2000. However there are issues regarding accurate ingredient lists, botanical nomenclature of the medicinal herbs, processing and product's quality. In the UK the Medicines and Healthcare medicaments Regulatory Agency takes nearly about 20,000 yellow card reports per year but this includes only about 100 herbal reports. Notwithstanding efforts to increase reporting by extending to nurses, pharmacists and consumers there hasn't been any significant increase in herbal

reports. Countries involving Sweden and Italy have carried out research work on herbal ADRs .Because there are few 'yellow card' herbal reports in the UK, it is relatively easy to identify adverse effects of discuss by evaluation of the individual reports without waiting for statistical signal detection. Where medicines are regulated, then manufacturers have pharmacovigillance obligations under European directives and additional National regulations. These requirements are the same for herbal medicines. This includes timetable and other reporting requirement for intimating the regulatory authorities of any reports of unwanted or unexpected side effects of their products. Without license or non-regulated products or dietary supplements don't have to comply with this directive**.**

***Issue with spontaneous reports:-***

**U**nderreporting is a well understood problem with spontaneous reporting systems. It is thought that this is same as to be a greater problem with herbal medicaments.

Factors Involved to under-reporting of herbal ADRs include:

• Lack of association between herb and adverse effect.

• Patient discontinues using the herbal medicine when they feel unwell.

• Physician/patient sometimes not aware of that herbal ADRs should be reported.

• Physician and RMP aren't aware of the use of herbal medicines as patient doesn't consider herbal and nutritional products to be 'medicines' and does not disclose use

The usefulness of any report of adverse events is dependent on understanding which herb was used. This helps in the accurate identification of the herb by the reporter. If non-appropriate names are used this can lead to confusion. For example if only 'digitalis' is used in a report this may refer to digitalis purpurea or digitalis lutea.The usefulness of ADR reports can be enhanced by co-working with pharmacognosy departments, botanic gardens or other toxicological units. Through which the identity of the medicinal herbs can be assured. When Adverse reactions are published in medical journals or submitted to the legal authorities then there are some confidence in the botanical identity.

Well established use or products registered under the Herbal Medicinal Product Directive will have brand name and the correctly listed constituents. Getting proper and corrected list of ingredients is problematic for unregulated/unlicensed products. Low quality products are a continuing concern as there is no assurity that the product contains the ingredients listed on the label. Herbal products adulterated with pharmaceutical medicines for inflammatory conditions (steroids, nsaids) or erectile dysfunction (sildenafil) is an international problem. In a reviewed study of herbal safety issues for 2010, found that pharmaceutical contamination or adulteration accounted for 336 of 390 warnings that were issued by regulatory authorities in UK, US, Canada, Singapore, Hong Kong and Australia. With few numbers of ADR reports in a single country, then herbal signals of interest may not be identified, merely for reactions that are rare. The WHO Collaborating Centre for Monitoring Drug Safety (UMC) looks for addressing this problem by collating ADR reports from over 100 countries around the world. By early their database contained over 6 million drug and herbal report. They have attempted to notify the nomenclature problems as herbal reports come from countries with different systems of traditional medicines. However because of the variance in the composition of different herbal products caution is needed when combining reports on a single herb/product..

***Some other methods of monitoring:***

Prescription event monitoring (PEM) is a non-interfering hypothesis making method for studying a drug once it is placed on the market by monitoring of individual prescriptions. An improved protocol of using PEM for herbal medicines have been developed based on monitoring case papers from herbal practitioners. It is a good method for finding specific safety concerns on use of frequent medicinal herbs. Intensive monitoring plans can be an up gradation of the spontaneous reporting schemes and are utilized to stimulate reporting on specific medication. In Thailand there is an extensive list of registered herbal medicines that are also used in hospital settings. They were used intensive monitoring on different varieties herbal products where there was a need for further safety knowledge. One other source of pharmacovigillance and safety information on herbal medicines is the Poisons Control Centers. In Europe and US these centers collect enquiries where there are concerns about the safety of a herbal medication or where there is a suspected poisoning. These enquiries are unnesseccarily formal reports for supporting information, involving product details, time duration and dosage may be lacking. Often the patients may have taken an acute or chronic overdose and are finding medical attention; this may not yield useful information on medium- or long-term toxicities. Poisons Control Centers are the most important source for dietary supplement ADRs in the US, was shown by a study carried out in 2008 which revealed that the primary reporting portal MedWatch, taken fewer reports than the poison centers. Other pharmacoepidemiological techniques for more detailed investigation of drugs that can also be used for herbal medicine safety including case control and cohort studies. These can be used to test findings developed after signals are detected using spontaneous reports. One such signal was identified from the reports of possible liver injury associated with the use of herbs. A pilot case control study was required to demonstrate that there was decreased association with liver injury and any individual herb, that has been under-utilized for herbal medicines.

***The WHO International Drug Monitoring Programme***

In co-ordination with the WHO International Drug Monitoring Programme, national pharmacovigillance centers designed by the competent health care authorities, that are responsible for the collection, processing and evaluation of case reports of suspected adverse drug reactions provided by health-care personnel. The Programme is given in two parts: Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigillance centre (1), chapters 7 and 8; and the requirement of pharmacovigillance: safety monitoring of medicinal products (5), especially chapters 3 and 4. Nowadays the Programme comprises a network of more than 70 national pharmacovigilance centers that are operating independently, but whose workings are coordinated and facilitated by WHO and UMC. UMC maintains the global WHO database to which all case reports received by the national pharmacovigilance centers are sent. UMC utilizes the global WHO database to detect signals of new adverse drug reactions from the cumulative data and to communicate risk investigations back to the national pharmacovigilance centers and to others dealing with drug safety

***1.5 Functions of national pharmacovigilliance centres***

Non-stop collecting the reports of suspected adverse drug reactions for medicines in the market. Assessment of case reports in sake of quality of documentation, causality assessment, coding to international standards utilizing the appropriate medication classification (the anatomical-therapeutic-chemical (ATC) classification), adverse drug reaction classification (WHO Adverse Reaction Terminology (WHO-ART)) and the Medical Dictionary for Drug Regulatory Activities (MedDRA) , clinical relevance , quality control, in particular identification of duplicate reports.Transformation in specific format of the assessed findings to UMC Generation of hypotheses or the identification of signals. These activities may be empowered by a research of the global WHO database (managed by UMC) for similar report studies. Communication of related safety information to the national and local regulatory authorities, health care professionals, pharmaceutical companies and other associates as appropriate. Further investigation of signals, risk factors or pharmacological mechanisms, receipt and communication as appropriate of safety information resulting from analysis by UMC and from regulatory authorities, case reports and the literature Provision of feedback to reporters , on time advice to health-care professionals and consumers on drug safety issues and managements.Education and training as well as Information sharing at regional/local and global levels.

## 2 Results and discussion:-

The whole review study aims to show that the pharmacovigilliance study is needed for the herbal products and its use in day to day life. As pharmaceuticals and biologicals uses post marketing survilliance as well as pharmacovigilliance reportings to prove the safety and efficacy of that particulars. While using the herbal products, there also chances of adverse effects. Therefore, the pharmacovigilliance study should be done for herbal medicines also.

## 3 Conclusion:-

Herbal medicines are mostly used in health care management in the world. However, in recent years, there have been several high-profile herbal safety concerns that have had an impact on the public health, and there is enhancing the need to develop pharmacovigilance (drug safety monitoring) systems for herbal medicines. Pharmacovigilance for herbal medicines is, in many respects and monitoring the safety of herbal medicines presents unique challenges. This review study wants to provide a comprehensive and critical overview of the current state of pharmacovigilance activities for herbal medicines at the national and global levels and showing future need of pharmacovigillance for the herbals. It will explore in depth the challenges that pharmacovigilance of herbal medicines presents, consider relevant emerging issues and what steps could be taken to improve safety monitoring for herbal medicines in the future.

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