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Pharmacovigilance of Herbal Medicine: A Review

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ABSTRACT

Pharmacovigilance plays a crucial role in gathering reliable data on the safety of herbal medicines used in Europe and the US. Current systems, designed for synthetic medicines, need adjustments to address the unique aspects of medicinal herbs. The use of traditional medicine from various cultures in these regions complicates matters, as even basic questions like herb naming systems and chemical variability prove challenging. Additionally, many people perceive natural or herbal products as inherently safe, causing the safety monitoring aspect to be overlooked due to the associated tag. Cooperation between orthodox physicians and traditional practitioners is necessary for comprehensive case details. Independent scientific support on toxicological investigations and botanical verification can significantly contribute to a thorough evaluation of case reports. Systematic pharmacovigilance is vital for accumulating reliable information on herbal medicine safety, enabling the development of appropriate guidelines for their safe and effective use.

1. INTRODUCTION:

As the use of herbal medications has grown, so have reports of potential toxicity and side outcomes. Such undesirable reactions can be caused by (i) side effects (usually detectable by pharmacodynamics and often predictable); (ii) reactions occurring as a result of overdose, over the duration, tolerance, dependence-addiction (detectable either by pharmacodynamics or pharmacovigilance); (iii) hypersensitivity, allergic, and idiosyncratic reactions (detectable by pharmacovigilance); and (iv) mid-term and long-term Because many herbal medications on the market have not been fully researched for pharmacology and toxicity, pharmacovigilance is critical in recognizing adverse responses.

As the usage of herbal medications has grown, so has the number of complaints of probable toxicity and adverse outcomes. Such undesirable reactions can be caused by (i) side effects (usually detectable by pharmacodynamics and often predictable);

(ii) reactions occurring as a result of overdose, over duration, tolerance, dependence-addiction (detectable either by pharmacodynamics or pharmacovigilance); (iii) hypersensitivity, allergic, and idiosyncratic reactions (detectable by pharmacovigilance); and (iv) mid-term and long-term Because many herbal medications on the market have not been fully researched for pharmacology and toxicity, pharmacovigilance is critical in recognizing adverse responses.

Furthermore, there is an ongoing concern with the unanticipated toxicity of herbal products owing to quality difficulties, such as the use of low-quality herbal material, improper or misidentified plants, wrong processing processes, and the provision of adulterated or contaminated herbs or products. To some extent, tighter legislation demanding GMP standards for manufacturing can alleviate these quality difficulties. However, medical herbs/items originate from a variety of nations with varying production standards and regulatory enforcement, thus low-quality goods are likely to persist.

The safety of herbal medications has been a concern for regulatory authorities, as significant side effects such as hepatotoxicity, renal failure, and allergic responses have been recorded. Recognizing the expanding relevance of herbal medicine usage across the world, the World Health Organization issued recommendations for monitoring herbal safety within the current pharmacovigilance framework (WHO, 2004).

2. Herbal pharmacovigilance challenges

Herbal remedies are used in Europe from a variety of traditions, including Chinese, Indian, North and South American, and African systems, as well as European systems. This variability contributes to the difficulties of herbal pharmacovigilance, such as determining the most appropriate herb naming system (botanical, common, pharmaceutical name, or herbal medication name) and validating the botanical identification of the herbal constituents. Normally, they are not a problem while monitoring synthetic medications. Some of these difficulties, such as name issues or adulterations, do not easily fit into existing pharmacovigilance systems or electronic data systems designed for medicines.

However, while certain changes may be required, building separate systems for herbals is not the solution since it is likely to increase difficulties and confusion if alternative forms or systems are utilized, perhaps lowering reporting rates even more. (Menniti-Ippolito et al., 2008). As an example of harmonization, the Uppsala Monitoring Centre (UMC) collects ADR complaints from over 100 countries worldwide, and its database contains over 4 million reports in 2010, over 21,000 of which include herbal or natural items. (UMC, 2011). These are all combined into a single database, with suspicious signals reviewed by professionals in relevant domains.

2.1 Particular difficulties

Herbal medications, unlike synthetic medicines, are often chemically rich and complex products rather than isolated single components.

A variety of factors can have an impact on the qualitative and quantitative chemical profile, including:

• Geographic origin - climate, soil, and photoperiod.

• The genotype.

• Plant parts such as leaves, stems, roots, root bark, and so on.

• Harvesting circumstances (year, season, and time of day).

• Preservation, processing, and extraction.

• Herb combinations and/or the processing of mixed herbs as medicines.

Because standardization of herbs in terms of active components is uncommon, this inherent heterogeneity results in products that may be extremely varied and not necessarily bioequivalent, even when derived from the same single herbal ingredient.

Combining reports of adverse effects (or efficacy) necessitates careful consideration of the differences or similarities in the chemistry or biological activity; however, if looking for safety signals for further investigation, studying groups of herbs containing similar compounds could be a potentially useful approach.

2.1.1 Herbal remedies and dietary supplements

Herbal product classification and regulation may differ between countries/jurisdictions. In the EU, they are categorized as herbal medicines (regulatory implications), with safety and quality criteria imposed. Some herbs may be sold as dietary supplements. Herbal products are classed as dietary supplements or botanicals in the United States, not as medications. Although the FDA adopted GMP criteria in 2007, quality will vary. Manufacturers are not required to report pharmacovigilance.

The legal distinction between dietary supplements and herbal medicine is nuanced. A medical product, in general, is described as "any substance or combination of substances presented as having properties for treating or preventing disease in humans." A dietary supplement, on the other hand, cannot claim to treat or prevent disease or to include a pharmacologically active chemical.

This may be a complicated subject because the same plant can be used as both a herbal medication and as a component in a nutritional supplement.

There are legal ramifications. Herbal medicines are licensed in Europe under two directives: 'well-established usage' or 'traditional herbal medical goods,' both of which have stringent quality (GMP) and safety criteria. (Amongst others). Food supplements do not have the same legal quality control standards as food. The classification of a herbal product as a food or medication may therefore have a significant influence on pharmacovigilance.

2.2. Nomenclature and terminology

Adverse reaction reports are worthless unless the medicinal herb(s) or components in a product can be identified. The Latin scientific name, the common or vernacular name, the pharmaceutical name or pharmacopeial name, or the particular herbal medication names (as

used in Traditional Chinese Medicine (TCM)) are all names for medicinal plants. Depending on the source and regulatory status of the product, herbal prescriptions, product packaging, or labels may contain one or more of these (or no label at all). These must be taken with caution because even scientific names may have synonyms.

The common or vernacular name is the least exact, and the same name may be used for plants belonging to various genera or species, thus it should be avoided if at all feasible. However, in Europe and the United States, the common name is widely used as a reference, despite the fact that EU requirements require the Latin scientific name to be labeled. If the product is of pharmacopeial quality, the species and plant component identification will be defined in the European Pharmacopoeia (PhEur). When applied to raw plant material or unlicensed herbal remedies that are not PhEur compliant, the popular term may be deceptive or confusing.

To minimize ambiguity, the genus, species, and portion of the plant should be stated somewhere on the product or packaging of the crude material. Unfortunately, a botanically correct label does not guarantee that the product includes the ingredients specified on the label. In situations of significant adverse reactions when particular toxins are suspected, laboratory testing of the product/herb may be recommended to validate the findings.

2.2.1 Initiatives addressing nomenclature and quality issues

There is presently no one reference list of medicinal plants that provides an official opinion on their current scientific name while also linking all synonyms of those plants available in the literature. Only Latin scientific names (e.g., Bupleurum chinense DC.) are standardized; this is done through the 'International Code of Nomenclature of Algae, Fungi, and Plants.' (ICN formerly ICBN).

The Royal Botanic Gardens Kew's new Medicinal Plants Names Index (MPNI) will solve this issue. One of the major goals of this project is to provide an authoritative index of scientific plant names linked to commonly used vernacular, trade, and pharmacopeia names in order to facilitate the creation of worldwide, industry-wide medicinal data standards. This is a three-year initiative (supported by the Wellcome Trust) that will be freely accessible over the Internet, with a variety of supplementary information services being built to meet specific requirements.

To facilitate worldwide reporting of herbal ADRs, the UMC collaborated with the Royal Botanic Gardens Kew and Uppsala University to create proper standards and cross-

referencing of herbal names for their database. A review of possible signals in the UMC database clearly demonstrates the complexities and issues of herbal pharmacovigilance, ranging from identifying what was utilized (plant, plant component, extract, dosage) to clinical data accessible from various nations. Following that, the UMC created the WHO Herbal Dictionary, an international reference source of herbal medicines meant to be used for coding and analyzing medication safety data both before and after commercialization.

There are several attempts underway to address botanical identification and establish quality standards. In addition to specific country pharmacopeias (for example, the British Pharmacopoeia), the European Pharmacopoeia is developing a large number of herbal monographs, including plants from China and the Indian subcontinent. In addition, the European Medicines Agency is working on herbal monographs. Herbal monographs have also been issued by the American Herbal Pharmacopoeia, USP, and the World Health Organization. (5 volumes).

These monographs can set plant quality standards; but, for them to be successful, they must be accompanied by adequate regulation and enforcement to ensure application. GMP is required in Europe for all registered herbal goods (well-established usage or traditional herbal products). Although this should enhance the general quality of herbal goods on the market, unscrupulous dealers may offer subpar items over the Internet, mail order, or other unregulated supply channels. Products marketed as meals or supplements will also be exempt from GMP regulations.

2.3. Herbal medication source users

Consumers tend to self-prescribe herbal remedies without contacting a professional herbal practitioner or other health professional, according to surveys. Products can be purchased without consulting a health professional from pharmacies, supermarkets, marketplaces, or the internet. Herbal medications are prescribed by conventional medical practitioners in a few European nations, including Germany. Consumers may be unaware that the bad effects of herbal medications can be reported to their medical practitioner or that regulatory authorities can be contacted. Furthermore, customers may not link the herbal product with the impact.

Some customers will seek herbal practitioners, however, legislation governing who can offer herbal remedies varies greatly across Europe. From highly qualified experts to unskilled and uncontrolled persons, training and practice standards differ.

3. Recognizing unfavorable reactions

The categorization of adverse responses is widely established in conventional medicine and also applies to herbal treatment.

According to Edwards and Aronson (2000), adverse responses are characterized as follows:

Type A (acute/augmented); dose-related and described by plant pharmacology.

Type B (bizarre/idiosyncratic); not dose-related or pharmacologically predictable.

Type C (chronic/cumulative): the effect is cumulative.

Type D (delayed onset) mutagenic, genotoxic

Herb safety is primarily based on practical experience, and it is efficient in diagnosing acute toxicity with symptoms that appear within hours or days after using any herbal therapy. This conventional expertise, however, is ineffective in identifying herb(s) that produce cumulative, chronic, or delayed toxicity. If the first evidence of detrimental effects does not appear for months or years after starting or discontinuing usage of the herbs/drugs, the use of the herbs is likely to be forgotten.

Aristolochic acid nephropathy (AAN) is a classic case of chronic poisoning. (Type C). The effects are cumulative, and kidney problems may appear up to two years after discontinuing the usage of the herbs. Although aristolochic acids were known to have the potential to cause renal toxicity, various species of Aristolochia have been used in traditional medicines of many countries. Only because of a cluster of cases in Belgium with comprehensive follow-up was the pattern of toxicity recognized and defined, complete with histological description, details of illness course, and the likely development of urothelial carcinomas.

Idiosyncratic reactions (Type B) can occur within days or weeks of starting a medicine but are difficult to identify because they are unpredictable, not dose or time-dependent, and are not always related to pharmacological activities but can result from reactive metabolites and immune-mediated reactions. Such responses occur seldom (>1:10,000 and 1:1000), but they are noteworthy since they can be dangerous or even lethal. Drug-induced hepatotoxicity is frequently caused by an atypical response. Because symptoms may be non-specific and there is no clearly identified poisonous ingredient that can be quantified in laboratory analysis, it is difficult to substantiate single case reports of suspected herbal toxicity that may be

attributable to idiosyncratic responses. Without a systematic reporting mechanism, such infrequent adverse effects will go unnoticed.

4. Pharmacovigilance techniques

For post-marketing medication safety monitoring, a variety of approaches are utilized, including spontaneous reporting and prescription event tracking. These approaches can be used to monitor herbal safety, but they must be modified to handle specific difficulties such as botanical nomenclature, quality, adulteration, labeling issues, prescriber/reporter disparities, and under-reporting.

4.1. Spontaneous reports

Medicine safety is often evaluated through spontaneous reporting mechanisms. Although there are small variances between nations, the basics remain the same. Medical professionals, including physicians, pharmacists, nurses, and, in certain countries, consumers, utilize standardized forms to report potential adverse reactions to regulatory authorities. The reports are of ‘suspected' adverse responses, and the reporter is not required to confirm the link between medicine and effect.

The reporting centers evaluate such causation on a case-by-case basis. Statistical approaches are utilized to detect disproportionate reporting rates, which might serve as a warning indication. A ‘signal' just shows an unfavorable impact of interest that has to be evaluated and investigated further; the relationship to the medicine or plant is not verified.

Where items are controlled as medicines and are delivered by health professionals who are well-versed in the usage of this reporting system, spontaneous reports are more likely to be successful. Consumers may be unaware of the significance of reporting unpleasant consequences.

Where herbal medicines/natural products are sold as dietary supplements in the United States, health professionals and consumers can report potential adverse events to the FDA MedWatch program. The spontaneous reporting mechanism is known as the 'yellow card' method in the United Kingdom; blue cards are used in other nations such as Australia. In the United Kingdom, the yellow card was changed in 2000 to allow for the addition of herbals. There are still issues with proper component listings, botanical names of medicinal plants, processing, and product quality.

In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency receives over 20,000 yellow card reports every year, although only about 100 of them are herbal reports. Despite efforts to enhance reporting by including nurses, pharmacists, and consumers, the number of herbal reports has not increased significantly.

Herbal ADRs have been studied in countries like Sweden and Italy. Because there are few 'yellow card' herbal complaints in the UK, identifying adverse effects of concern by evaluating individual reports without waiting for statistical signal detection is extremely simple.

Manufacturers have pharmacovigilance requirements under European directives and maybe extra National rules where medicines are regulated (e.g., licensed as a well-established or traditional herbal medical product in Europe). These standards apply to both conventional and natural treatments. This includes deadlines and other reporting obligations for notifying regulatory authorities of any complaints of undesirable or unexpected adverse effects from their goods. This order does not apply to unlicensed or unregulated items or dietary supplements.

4.2. Issues about spontaneous reports

With spontaneous reporting systems, underreporting is a well-known issue. (Hazell and Shakir, 2006). This is regarded to be a more serious issue with herbal treatments. The following factors contribute to the under-reporting of herbal ADRs:

• There is no link between the herb and the negative impact.

• The patient discontinues use of the herbal treatment when they become ill.

• The physician or patient is uninformed that herbal ADRs must be reported.

• The physician is ignorant of the use of herbal medications since the patient does not consider herbal and nutritional goods to be "medicines" and does not reveal their usage.

Any report of bad effects is only meaningful if you know what herb/product was taken. This is dependent on the reporting correctly identifying the product/herb. When insufficient names are used, this might lead to misunderstanding. If the word 'ginseng' is used alone in a report, it might refer to Panax ginseng C.A. Mey or Panax quinquefolius (Burk.) F.H. Chen.

However, it may also refer to a variety of different plants known as ginseng, such as Eleutherococcus senticosus (Rupr. & Maxim) Maxim (Siberian ginseng) or the unrelated Withania somnifera (L.) Dunal. (Indian ginseng).

Collaboration with pharmacognosy departments, botanic gardens, or other toxicological units can increase the quality of ADR reports. The Chinese Medicine Advisory Service in the United Kingdom deals with inquiries about possible herbal ADRs. The identity of Chinese medicinal plants can be confirmed by collaboration with the Royal Botanic Gardens Kew. There is some trust in botanical identification when ADRs are published in medical publications or reported to authorities.

Herbal toxicity is investigated by the Hospital Authority Toxicology Reference Laboratory at Princess Margaret Hospital in Hong Kong.

Products with a long history of usage or those registered under the Traditional Herbal Medicinal Product Directive (THMPD) will have a brand name and the components specified appropriately. Obtaining reliable ingredient lists for unregulated/unlicensed items is difficult. Poor-quality products continue to be a source of worry since there is no guarantee that the product includes the substances specified on the label.

Herbal items contaminated with prescription pharmaceuticals for weight loss (e.g., sibutramine), inflammatory disorders (steroids), or erectile dysfunction (sildenafil) are a worldwide issue. In an examination of herbal safety alerts issued in 2010, we discovered that pharmaceutical contamination or adulteration was responsible for 336 of 390 warnings given by regulatory agencies in the UK, US, Canada, Singapore, Hong Kong, and Australia.

With a low number of ADR reports in a single nation, herbal signals of interest may be missed, especially for unusual responses. The WHO Collaborating Centre for Monitoring Drug Safety (UMC) is attempting to solve this issue by compiling ADR reports from over 100 countries worldwide.

By early 2011, their database had grown to include over 6 million medication and herbal reports. This is the most comprehensive archive of such reports. They sought to resolve nomenclature concerns as herbal reports came from nations with diverse traditional medicine systems. However, because the content of different herbal products varies, care is advised when aggregating reviews on the same herb/product. Groups of herbs with similar chemical compositions, on the other hand, can be utilized to identify signals for further research.

5. Monitoring for herb-drug interactions:

Herbal medicines are seen to be safe, even when taken alongside pharmaceutical medications. Herbs can be utilized to cure the underlying ailment or to mitigate the negative effects of conventional treatment. Under-reporting of potential interactions between plants and medicines is a growing problem, and it stems from the same reasons as herbal ADR under-reporting.

The specific issues that must be addressed are those that may affect certain patient groups, such as cancer patients, where the rate of combining conventional and herbal medication usage is anticipated to be high and the danger of interaction is large. Patients on treatment regimens comprising powerful pharmaceuticals metabolized by cytochrome P450 enzymes or whose bioavailability is modified by P glycoprotein are more likely to have herb-drug interactions.

Adverse effects caused by interactions may go unnoticed if the physician or other health professional is unaware of the concurrent use of medicinal herbs. Adverse medication interaction responses are rather prevalent; however, they are largely avoidable. Recently, the UMC conducted research to demonstrate that pharmacokinetic and pharmacodynamic medication interactions may be discovered in their database. It is intended that as this investigation progresses, herb-drug interactions will be examined.

6. Additional monitoring mechanisms

Prescription event monitoring (PEM) is a non-interventional hypothesis generation approach for investigating a medicine after it has been placed on the market, based on individual prescription tracking. Based on monitoring prescriptions from herbal practitioners, a modified methodology for employing PEM for herbal medications has been created in the United Kingdom. It is an effective tool for exploring particular safety issues about commonly used therapeutic plants.

Intensive monitoring plans can be used to encourage reporting on certain drugs and are an extension of spontaneous reporting initiatives. There is a long list of recognized herbal medicines in Thailand that are also utilized in hospitals. They employed thorough monitoring of 9 distinct herbal items when more safety information was required. Poisons Control Centres are another source of pharmacovigilance and safety information on herbal

medications. In Europe and the United States, these centers handle inquiries concerning the safety of a product or a suspected poisoning.

Because these inquiries are not always formal reports, supporting information such as product specifics, time course, and dose may be absent. Often, people seek medical assistance after taking an acute or chronic overdose; this may not provide helpful information about medium- or long-term toxicity. Poisons Control Centres are a key source of dietary supplement ADRs in the United States, according to a 2008 research that found that the principal reporting site, MedWatch, got fewer reports than the poison centers.

Case control and cohort studies are two more pharmaco-epidemiological methodologies that may be used to investigate the safety of herbal medicines. These can be used to evaluate hypotheses that have been generated after signals have been noticed via spontaneous reporting. One such signal was discovered in reports of probable liver damage connected with the use of Chinese medicines. A pilot case-control study was utilized to show that there was no increased relationship between liver damage and any specific herb. These approaches have thus far been underutilized for natural medicines.

7. Practitioners of herbal medicine

Herbal practitioners may be a helpful source of ADR information, however, due to differing degrees of professional regulation in Europe, they are not always recognized as ADR reporters.

Some herbal practitioner organizations have set up their own reporting systems, which are not always linked to formal institutions. Reporting by skilled herbal practitioners has advantages.

They are educated in the use of medicinal plants and should be able to recognize the unanticipated consequences of the therapy as well as the activities and potential toxicity of the herb. Herbal prescriptions are frequently altered in order to prevent negative effects or enhance results. Although some consequences may be minimal, nonspecific symptoms (such as fatigue and liver failure) may signal a more serious condition. Because they serve a small number of patients in Europe, they may miss unusual adverse outcomes. Practitioners are less likely to disclose suspected ADRS in countries where herbal practice is not widely recognized or has a low professional standing. Clear definitions of reportable ADRs must be developed and standardized across jurisdictions.

8. Minimum ADR standards

Various groups have developed criteria for reporting adverse events and clinical studies, including herbal products. Patient demographics (age, gender), relevant medical history, symptoms, abnormal laboratory values, drug identification, rationale for usage, dose, time course (length of use, start of symptoms), and details of adverse event are all required for case reports. They comprise the following information for produced herbal products: product name, manufacturer, batch number, kind and concentration of extract, and concentration of any standardized ingredients.

Botanical identification is limited to the Latin scientific name, plant parts, and preparation. (Herb or extract). These rules, however, are insufficient for herbal medications delivered in complicated formulations, as well as most traditional medicines used in Europe, such as Chinese or Ayurvedic medicine. Any ADR report should include the name as it appears on the label/prescription. If further information about identification is obtained by morphological or chemical analysis, the source of this information should be indicated. The plant name is not always included in traditional herbal formulae (or even goods). The Latin scientific name cannot be inferred from the common or drug name, and it is only correct if the plant material has been validated.

Once the plant's identity has been confirmed, the scientific name, author, plant component, and processing should be provided. Details regarding the herbal material's processing prior to use (e.g., in Chinese medicine, stir-frying, steaming) are essential since this might substantially modify the chemical profile or bioavailability of the herbs.

The herbalist makes a diagnosis. This should be based on information provided by the practitioner. Involving a herbal practitioner in any evaluation of a possible adverse response might give an important history or understanding of the herbs' usage.

Accurate adverse reaction reports are necessary in order to identify true adverse events and provide relevant warnings and guidance to practitioners and patients. If possible adverse responses are not carefully analyzed, or if the herbs are erroneously identified,'safe' or helpful plants may be banned wrongly. To avoid misconceptions, accurate identification of the therapeutic plants employed is required when publishing case reports in the medical literature.

As the use of herbal medications has increased throughout the world, there has been a dearth of knowledge on the safety of herbs as they are used in diverse patient groups that may differ in critical factors such as pharmacogenomics and metabolization profiles, or gut microbiota composition and bioactivity. Effective pharmacovigilance is required to collect accurate information on the safety of herbal medications in order to produce adequate guidelines for safe and effective usage.

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