



Pharmacovigilance of Natural Herbal Medicines Research for Efficacy, Safety and Quality Assurance of Phytomedicine Products

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ETF, CNF, DJF, LBF and MTAO designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors RNM and NK managed the analyses of the study. Authors ER, TBA, NK, RD and ABY managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Improved traditional medicine/phytomedicine formulations have gained a global acceptability and popularity as therapeutic agents for many diseases in Sub-Saharan Africa. Herbal products are generally considered as safe, environmentally friendly and increasingly consumed by the community without prescription. There is a lack of systematic data on traditional medicine-associated adverse effects due to complex issues such as products with multiple ingredients, poor standardization, lack of clinical trials, variation in manufacturing processes, contamination, adulteration and misidentification of herbs. The aim of pharmacovigilance is to detect, assess, understand, and prevent the adverse effects or any other possible drug-related problems, related to herbal, traditional and complementary medicines. Pharmacovigilance for herbal medicines is in its infancy, and monitoring the safety of natural products presents unique challenges, and as such, preparations are available from a wide range of sources where limited qualified healthcare professionals are available. The ethico-legal issues and regulatory approval mechanism of herbal medicine vary from country to country. This paper also elucidates the level of challenges associated with herbal pharmacovigilance geared towards improving safety monitoring for herbal medicines in the future.

Keywords: Pharmacovigilance; herbal medicines; improved traditional medicine; regulation; research.

1. INTRODUCTION

The World Health Organization (WHO) has elaborated guidelines for the assessment of the safety, efficacy and quality of herbal medicines as a prerequisite for global harmonization [1]. The Medicines and Healthcare products Regulatory Agencies of UK has launched a 'yellow card' scheme for ADR reporting for monitoring the safety of herbal medicines. Like many other countries particularly in the developing countries, the Cameroonian Drug Regulation Agency (CDRA) is yet to fully integrated traditional herbal medicine into all aspects of health care system despite the effort put in place to develop a strategic plan for its integration. Herbal pharmacovigilance should be implemented in Cameroonian herbal regulatory system to access various aspects of adverse drug reactions (ADRs), delayed or acute toxicities, allergies etc. associated with single herb and/or polyherbal formulation [2]. Modified spontaneous reporting forms are to be designed following WHO template to collect information on suspected ADRs of herbal medicines with the aim of achieving the ultimate goal of providing available safer and more effective treatment available to patients. This review is intended to provide a critical analytical overview of the current state of pharmacovigilance for Cameroon's herbal medicines both at national and global levels.

From prehistoric times, herbal medicine has been used by multiple communities and civilizations throughout the world. For the past

five decades, herbal medicines have been increasingly consumed by people without prescription [1]. Herbal formulations have reached widespread acceptability as therapeutic agents. They are traditionally considered as harmless since they belong to natural sources and most over-the-counter herbal products like ginseng, moringa have attracted a lot of public attention. However, there are several case reports of adverse reactions of herbal drugs, erroneously considered safe as mentioned in the literature. However, ADRs and hazards of herbal medicines as self-prescriptions have been well recorded. The accurate scientific assessment of herbal medicine is a requirement for global harmonization of herbal health claims. It is in this direction that the WHO has set specific guidelines for the assessment of the safety, efficacy and quality of herbal medicines [2,3]. The purpose of pharmacovigilance is to detect, assess understand, and to prevent the adverse effects or any other possible drug-related problems, which is not only confined to chemical drugs, but extended to herbal, traditional and complementary medicines, biologicals, vaccines, blood products and medical devices [2,3].

1.1 Pharmacovigilance

Pharmacovigilance (PHV), a French term referring to identifying side effects of drugs, their treatment, documentation, reportage and regulatory decisions based on them, is a well-established science in the developed world [4]. Pharmacovigilance is the pharmacological science relating to the detection, assessment,

understanding and prevention of adverse effects or any other drug related problems, particularly long term and short-term side effects of medicines [5]. Generally, pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines. Safety and efficacy are the two major concerns about any drug. While the efficacy of a drug can be detected relatively easily, the same cannot be said about safety because the adverse effects of a drug may be uncommon, but very serious. Many patients may be affected or exposed to a potential risk before the relationship with the drug is established [2,6]. Today, the concern of PHV have been widened to include herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines [3,7]. It is fast emerging as an important approach for the early detection of unwanted effects of the drugs and to take appropriate regulatory actions if necessary, to ensure the safer use of drugs.

1.2 Risk Associated with Medicines

Efficacy is the extent to which a drug works under ideal circumstances in clinical trials. Effectiveness is the extent to which a drug works under real world circumstances of clinical practice. Medicines have helped to improve health and extend the life of human beings. Medicines affect the lives of hundreds of millions of people every day, but they also produce adverse effects on the human body from time to time [7]. There are risks in any xenobiotics introduced into the human body, whether chemical or surgical, nothing is entirely predictable. While most of the drugs are precisely targeted to the causes and mechanisms of disease, they may also have minor or major distressing effects on other human body organs, or interact negatively with the systems of the particular individual [8]. No drug can be guaranteed to be safe beyond a certain limit, as any drug can be toxic in higher.

2. NEED OF EFFECTIVE PHARMACOVIGILANCE SYSTEM IN CAMEROON

Pharmaceutical companies in all countries are required by law to perform clinical trials, that is testing new drugs on human before they are made generally available. The manufacturers or their agents usually select a representative

sample of patients for whom the drug is designed, at most a few thousands along with a comparable control group [2,8]. The control group may receive a placebo and/or another drug that is already marketed for the disease. The purpose of clinical trials is to disclose efficacy, any harmful effects and its benefit-harm-risk profile. Clinical trials provide information which should be reliable for larger populations with the same characteristics as the trial group - age, gender, state of health, ethnic origin, and so on [9]. The variables in a clinical trial are specified, controlled, and the results relate only to the population to which the trial group is a representative sample. A clinical trial can never explore the whole story of the effects of a drug in all situations determined by legislation and by contemporary judgements about the acceptable balance of benefit and harm due to the following indicated shortcomings [10].

- ✓ Limited value of animal experiments in predicting human safety.
- ✓ Clinical trials are limited in time and number of patients.
- ✓ Patients are selected considering various factors and conditions (adults, no other drugs, no other diseases).
- ✓ Results are not truly representative of real-life use.
- ✓ Rare or delayed serious reactions are likely to remain unnoticed.

Pharmacovigilance is a useful tool in post-marketing surveillance, to identify, evaluate and respond to ADRs and safety issues about medicinal products. Pharmacovigilance is a new emerging area in Cameroon and it is imperative to develop capacity as well as competence. The regulatory agency (National Drug Regulatory Agency) within the Division of Medicine and Pharmacy, are increasingly becoming proactive in seeking out potential safety issues with marketed drugs. Political and social pressures in Cameroon have increased alongside with faster communication channels. Litigation due to the lack of pharmacovigilance can be devastating for all concerned. Failure to practice pharmacovigilance can lead to the suspension or withdrawal of the license of pharmaceutical companies or drug withdrawal in the Cameroonian medical product market [11].

2.1 Functions of Pharmacovigilance

The monitoring of adverse effects of drugs and herbal remedies as they are used in the population are called post marketing

surveillance. Good Vigilance Practice (GVP) defines pharmacovigilance as side effect surveillance of a drug in post marketing safety surveillance. Pharmacovigilance is therefore one of the important post-marketing tools in ensuring the safety of pharmaceutical and related health products. According to WHO Guidelines (2000), the functions of pharmacovigilance are:

- Proactive monitoring and reporting on the quality,
- Ascertain safety and efficacy of drugs
- Detection and study of adverse reactions
- Measurement of risk
- Measurement of effectiveness
- Benefit and harm evaluation
- Dissemination of information, education, early warning, rational and safe use of medicines
- Monitoring the impact of any corrective actions taken
- Providing information to consumers, practitioners and regulators on the effective use of drugs
- Designing programs and procedures for collecting and analyzing reports from patients and clinicians

2.2 Pharmacovigilance in Cameroon

Cameroon is a country with a population of over 20 million people [12], where various contemporary systems of medicine like Allopathy, Homoeopathy, herbalism etc are practiced. In the absence of a monitoring and reviewing process, the adverse effects, interactions and misuse of drugs can have a negative consequence on the health system in the country [13]. ADR monitoring programs are not new to Cameroon. In the last two decades, many drugs have been withdrawn from the market because of serious ADRs. Very recent example of a drug being banned due to severe cardiovascular side effects in Cameroon after its withdrawal by manufacturer is Cox-II inhibitor and anti-inflammatory drug rofecoxib which has reportedly caused 93,000 heart attacks in users worldwide. To promote the importance and benefits of pharmacovigilance, the pharmacy and medicine division of the Ministry of health. The directorate for pharmacy, laboratory and drugs of the government of Cameroon launched the National Pharmacovigilance Program (NPP) in 2005. It is largely based on the recommendations of the WHO's Safety Monitoring of Medicinal Products - Guidelines for Setting Up and Running a Pharmacovigilance Centre". Under this program,

the whole country is supposed to be divided into zones and regions for operational efficiency. The National Pharmacovigilance Program (NPP) for Cameroon, besides its infancy, was initially sponsored by the WHO. The NPP aiming to foster the culture of adverse drug event reporting also focus on the following subsequently:

- Generate broad ADR data on the Cameroonian population and share the information with global health-care community through WHO-UMC (Uppsala Monitoring Center)
- Ensure optimum safety of drug products in the Cameroonian market
- Provide technical expertise for evaluating statutory adverse event reports furnished by Sponsors conducting clinical trials in Cameroon.

The National Pharmacovigilance Advisory Committee (NPAC) oversees it.

ADR reports can be sent only by health care workers (doctors including dentists, nurses, pharmacists) to any one of the pharmacovigilance centers. These centers are not well mapped out and functional in Cameroon.

2.3 The Objective of the National Pharmacovigilance Centers

Monitoring the ADRs of medicines in order to identify previously unexpected ADRs or indications or certain reactions that occur more commonly than previously believed. This include the collection, review and evaluation of all spontaneous ADR reports received by the unit on a nation-wide basis, and keyed into the ADR database for aggregate analysis. These reports are also submitted to the WHO, International Drug Monitoring Program for international collaboration on drug safety [13].

- Review Periodic Safety Update Reports (PSURs) submitted by pharmaceutical companies required to be submit for all new chemicals' drugs. PSURs shall be expected to be submitted every 6 monthly for the first 2 years of marketing in India, and annually for the subsequent 2 years.
- Maintaining contacts with international regulatory bodies working on pharmacovigilance and exchange of information on drug safety.
- Assessing the regulatory information relating to safety in order to determine

necessary action to be taken to assure safe use. Based on the available data, the Advisory Committee should make recommendations on product label amendments, product withdrawals and suspension.

Providing information to end-users through ADR news bulletins, drug alerts and seminar.

3. PHARMACOVIGILANCE FOR HERBAL PRODUCTS

Herbal medicines are widely used in health-care in both developed and developing countries. 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 increasing emphasis on the need to develop pharmacovigilance systems for herbal medicines. Pharmacovigilance for herbal medicines is, in many respects, in its infancy and monitoring the safety of herbal medicines presents unique challenges [14]. The associated safety risks of some herbal medicines are considered to be low but the acquired knowledge on the relative safety of herbal medicines remains poor. Standard pharmacovigilance tools have additional limitations when applied to herbal medicines. Adverse effects may be reported as being attributed to a pharmaceutical drug even when it has been taken concomitantly with an herbal product. Inefficiencies in pharmacovigilance procedures invariably lead to the relative underreporting of adverse effects [6]. Pharmacovigilance studies on herbal medicines have been studied by many authors in other countries such as Iran, Nigeria and sub Saharan Africa [15,16,17].

3.1 Safety Issues Associated with Herbal Medicinal Products

The uses of traditional and complimentary medicines are increasing rapidly in developed countries. Policy makers, health professionals and the general public all over the world are concerned with question about the safety, quality, availability, preservation, standardization and further development of this health care system [15]. Despite the immense potential of traditional therapies, many of them remain till date untested and uses are not properly mentioned in the labels as a result of this knowledge about their potential side effect are limited. The substitution for example of toxic *Aristolochia species* in traditional Chinese medicines has resulted in a case of serious renal toxicity and renal cancer in

Europe, China and America [7]. There are some diverse issues related to safety of traditional herbal medicines that has led to the development of a pharmacovigilance system in most countries. [18]. PHV studies has contributed significantly to ethnobotanic and ethnopharmacological research, safety monitoring of herb drug interaction which is vital component of pharmacovigilance.

3.2 Quality Related Safety Issues

Generally, a particular plant genus could have several species that are used medicinally, and also different parts of a particular plant has difference in phytochemical constituents [19]. Quality control of ethno traditional medicines is different and gives rise to public health concern since a majority of herbal products are unregulated. The problems include:

- Deliberate or accidental inclusion of prohibited or restricted ingredients
- Demand outstripping supply of good quality ingredient, the substitution of ingredients, The adulteration with heavy metals/ toxic elements and/or synthetic drugs
- Contamination with toxic substances
- The difference between labelled and actual content
- The lack of standardized manufacturing practice
- The lack of authentication and reproducibility of herbal ingredients
- The absence of information about safe usage
- Illegal or unauthentic claims

3.3 Self-Medication Issues

Myriads of herbal products are self-prescribed for minor as well as severe chronic diseases [8]. Self-medication is associated with serious health concerns like delay in effective treatment, interference with vital treatment, overloading patient with multiple medication, lack of communication with practitioner, weak or missing information and side effects or ADRs [4,20].

3.4 Intrinsically Toxic Constituents of Herbal Ingredients

Limited toxicological data are available on even widely used medicinal plants. Some intrinsically toxic plant constituents like in Aristolochic acid are a series of substituted nitrophenanthrene carboxylic acids, reportedly occur only in

Aristolochiaceae family have been shown to be nephrotoxic, carcinogenic and mutagenic [9,21]. Pyrrolizidine alkaloids present in a number of plant species notably *Crotalaria*, *Heliotropium*, and *Senecio* used as 'herbal tea' causes severe liver damage especially with an unsaturated nucleus [11] Mistletoe and Pokerooroot contains haemagglutinating and mitogenic lectins, cytotoxic and cardiotoxic viscotoxin, and irritant saponins causing gastrointestinal irritation [22], intense abdominal cramps and haematemesis. Cyanogenetic glycoside are present in kernels of a number of fruits including cassava, bitter almond, pear, palm seeds, rubber etc. They release hydrogen cyanide on gastric hydrolysis following oral absorption which causes respiratory failure [23,24]. Furanocoumarins found predominantly in Umbelliferae and Rutaceae have been reported to be phototoxic causing severe skin burns. Excessive ingestion of Ginseng and Liquorice can result in edema and hypertension [13-15].

4. HERB-DRUG INTERACTION

Interaction between herbal drugs and conventional medicines is gaining increasing concern due to report of some potential interactions [13]. The emergence of significant problems associated with ingestion of grapefruit juice concurrently with certain medicines has emphasized the fact that clinically relevant interaction can occur between drugs and natural products [14] St. John's Wort reduces therapeutic efficacy of a number of drugs by inducing hepatic microsomal P450 enzymes interfering with indinavir, warfarin, digoxin, theophylline and oral contraceptives affecting efflux P-glycoprotein [15] Reports have been made of herbal products cross reacting with diagnostic markers in therapeutic drug monitoring [16].

4.1 Specific Patient Group

It is medically advised that no medicine should be taken during pregnancy unless the benefit to the mother outweighs any possible risk to the fetus. This generally however is not observed in case of herbal medicines as they are promoted to be natural and completely safe alternative to conventional medicine [17,25] Some volatile oils containing triterpenoid constituents can act as abortifacient [18]. Herbal ingredients like fenugreek, motherwort, raspberry etc have spasmolytic action. Some herbal tea contains laxative ingredients such as senna, frangula and cascara that must not be used while pregnant

and with care in breast feeding ones. Herbal remedies should therefore be used with caution in children, elderly patients, patients with cardiovascular disease and perioperative persons [19,20].

4.2 Under Reporting of ADRs to Herbal Medicines

The general public and patients do not have an attitude to consult a doctor before taking herbal remedies or report adverse reactions. Greater public awareness is needed towards improved reporting of such reactions in particular with regards to the precise identity and composition of the products [25].

4.3 Need of Pharmacovigilance for Herbal Medicinal Products

WHO defines traditional medicine as including diverse health practices, approaches, knowledge and beliefs incorporating plant, animal, and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness [2,26]. The inclusion of herbal medicines in pharmacovigilance systems is becoming increasingly important given the growing use of herbal products and herbal medicines globally. As an immediate response to the need for pharmacovigilance for herbal medicines, WHO has increased efforts to promote herbal safety monitoring within the context of the WHO International Drug Monitoring Program [27]. WHO survey showed that around 90 countries, less than half of WHO's Member States, currently regulate herbal medicines, and a smaller proportion even have regulatory and/ or qualification systems for herbal medicines providers [28].

5. CHALLENGES ASSOCIATED WITH PHARMACOVIGILANCE OF HERBAL MEDICINAL PRODUCTS

The Pharmacovigilance of herbal medicines exhibits particular challenges because such preparations are available from a wide range of outlets typically where there is no healthcare professional available, most purchases are in conventional over the counter (OTC) environment [11,29]. Against a background of limited regulatory policy for herbal medicinal products, safety issues also arise from poor-quality and inherently toxic products. There is a real need to monitor safety of herbal medicines

comprehensively [21]. There is a lack of research examining the quality of advice on herbal medicines given by doctors, nurses and other healthcare providers. It is well-known that users of herbal medicines do not often disclose the use of these products to healthcare professionals, and are not asked by healthcare professionals about their use of these products [30]. Even if the information on the use is provided, the knowledge of most healthcare professionals on these products is inadequate due to and/or lack of reliable sources of information to update knowledge (e.g. efficacy of specific products, interactions between herbal and conventional medicines) [31].

Underreporting of suspected herbal ADRs by healthcare professionals is possible also because of unawareness that spontaneous reporting systems will accept reports associated with herbal medicines, or not. At the same time the quality of herbal spontaneous reporting is of poor scientific value since common or vernacular names are usually used for herbal medicines [15]. If Traditional Medicine / Complementary and Alternative Medicine (TM/CAM) is to be promoted as a source of healthcare, efforts must be made to promote its rational use. The identification of the safest and most effective therapies will thus be "crucial" as quoted in WHO Traditional medicine strategy, 2002-2005. This guideline aims to propose to the member states a framework for facilitating the regulation of herbal medicines/ products used in traditional medicine. The regulation will cover issues like, classification, assessment of safety, assessment of the efficacy, quality assurance, pharmacovigilance and control of advertisements of herbal medicinal products [32].

5.1 Pharmacovigilance for Herbal Medicinal Products in Other Countries

Herbal medicines are the staple of medical treatment in many developing countries and are used for a wide range of ailments. Currently, in the United States, herbal products can be marketed only as food supplements, and a herb manufacturer or distributor cannot make any specific health claims without FDA approval [7,19]. Since herbal medicines are regulated as dietary supplements under the 1994, Dietary Supplement Health and Education Act (DSHEA), they are not subject to the premarketing regulatory clearance required for drugs. The burden of proof is on the U.S. Food and Drug Administration to show a dietary supplement is unsafe. This is in contrast to pharmaceutical

drugs, which cannot be approved until the manufacturer has demonstrated safety and efficacy [3].

In Australia a two-tiered approach to the regulation of therapeutic goods has been developed. This is essentially based on risk, where listed medicines are considered as posing a lower risk than fully registered medicines. Most complementary medicines including herbal medicines are listed. Herbal medicines are assessed as low or high risk depending on the toxicity of the ingredients, proposed dosage, appropriateness of the indications and claims for self-diagnosis and management, and the potential for adverse reactions [32].

Registered medicines are individually evaluated for Quality, Safety and Efficacy before they are released onto the market. The Therapeutic Goods Administration individually assesses listed medicines for compliance with legislation and they are not evaluated before release. Listed herbal medicines may only have indications and claims that are for the symptomatic relief of non-serious conditions, or for health maintenance, health enhancement and risk reduction [33]. Under the Australian risk management measures, low risk herbal medicines are allowed early market access and are supported by appropriate post-market regulatory activity. In Japan, China, Korea, and India patent herbal remedies composed of dried and powdered whole herbs or herb extracts, are in common therapy [21]. Traditional herbals are the backbone of China's medicine, managed by the State Administration of Traditional Chinese Medicine. Japan's traditional medicine, kampo, is similar to and historically derived from Chinese medicine also includes traditional medicines from Japanese folklore. In 1988, the Japanese herbal medicine industry established regulations to manufacture and control the quality of extract products in kampo medicine. Those regulations comply with the Japanese government's Regulations for Manufacturing Control and Quality Control of Drugs. In India, moves are being made to establish more effective regulation of quality, safety and efficacy (QSE) of Ayurvedic medicine [27,34].

6. METHODS IN PHARMACOVIGILANCE

6.1 Passive Surveillance Spontaneous Reporting

Spontaneous reporting is the core data-generating system of international

pharmacovigilance, relying on healthcare professionals to identify and report any suspected ADR to their national pharmacovigilance center or to the manufacturer. Spontaneous reports are almost always submitted voluntarily. Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. Spontaneous reports alerts to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies. It also provides important information on at-risk groups, risk factors, and clinical features of known serious ADRs [28,35].

The major weaknesses of this system is under-reporting, though the figures vary greatly between countries and in relation to minor and serious ADRs. Another problem is that overworked medical personnel do not always see reporting as a priority, and even if the symptoms are serious, they may not be recognized as the effect of a particular drug [30]. Even so, spontaneous reports are a crucial element in the worldwide enterprise of pharmacovigilance and form the core of the WHO Database, which includes around 3.7 million reports, growing annually by about 250,000 [36].

A case report is a notification from a practitioner regarding a patient with a disorder that is suspected to be drug-related. When different doctors independently report the same unknown and unexpected adverse experiences with a drug, it can be an important signal. There are certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome [3].

6.2 Other Reporting Methods

Some countries legally oblige spontaneous reporting by physicians. In most countries, manufacturers are required to submit reports they receive from healthcare providers to the national authority. Others have intensive, focused program concentrating on new drugs, even controversial drugs, along with the prescribing habits of groups of doctors involving pharmacists in reporting to generate potentially useful information [4].

6.3 Stimulated Reporting

Stimulated reporting is used to encourage and facilitate reporting of adverse events based on a

pre-designed method by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods. Such methods also include on-line reporting of adverse events. Stimulated adverse event reporting in the early post-marketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan) [36].

6.4 Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organized process. Active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients are asked to complete a brief survey form and give permission for later contact [32].

7. PHARMACOVIGILANCE SENTINEL SITES

Reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites can do active surveillance. The selected sites can provide information data from specific patient subgroups that would not be available in a passive spontaneous reporting system [7]. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients and increased costs. Active surveillance with sentinel sites is most efficient for drugs used mainly in institutional settings such as hospitals, nursing homes, hemodialysis centers etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs [23].

7.1 Drug Event Monitoring

In drug event monitoring, patients are mostly identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire sent to each prescribing physician or patient at pre-specified intervals to obtain

outcome information. Information on patient demographics, indication for treatment, duration of therapy, dosage, clinical events and reasons for discontinuation can be included in the questionnaire. More detailed information on adverse events from a large number of physicians and/or patients can be collected in this way. Limitations of drug event monitoring include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals [2,16].

7.2 Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). These registries can be used to collect a battery of information using standardized questionnaires in a prospective mode. Disease registries, as in blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other factors associated with a clinical condition [31]. A disease registry can also be served as a base for a case-control study to compare the drug exposure cases identified from the registry and the controls selected from either patient with another condition within the registry, or patients outside the registry. Exposure registries address specific populations exposed to drugs of interest. Patients can be followed over time to include in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can be useful for signal amplification, particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition [36].

7.3 Comparative Observational Studies

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. The main types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective) [23].

7.4 Cross-Sectional Study (Survey)

The data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status

constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. These studies are best used to examine the prevalence of a disease at a given time or to examine trends over time, when data for serial time points are captured when exposures do not change over time. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. The major drawback of cross-sectional studies is temporal relationship between exposure and outcome, which cannot be addressed directly [25].

7.5 Case-Control Study

Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions such as renal and hepatic dysfunctions that might modify the relationship between the drug exposure and the adverse event [9]. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. In a case-control study, cases of disease are selected and patients identified from an existing database or data collected specifically for the purpose of the study of interest. Controls, or patients without the disease or event of interest, are selected from the source population in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population of interest (the elderly, children, pregnant women, etc). The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups [32-34].

7.6 Cohort Study

Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. In a cohort study, a population-at-risk a disease is followed over time for the occurrence of the disease. Information on exposure status is collected throughout the follow-up period for each patient and incidence rates calculated [11].

However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest (such as an orphan drug) or to study

very rare outcomes. Like case-control studies, the identification of patients for cohort studies can come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through oversampling of these patients or by stratifying the cohort if sufficient numbers of patients exist [33].

7.7 Targeted Clinical Investigations

Based on the pharmacological properties and the expected use of the drug in general practice, specific studies can be conducted to investigate potential drug-drug interactions and food-drug interactions. These studies include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers. Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies [20]. Children, the elderly, and patients with co-morbid conditions might metabolize drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a drug outside of the formal/ traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large simplified trial might be conducted. Patients enrolled in a large simplified trial are usually randomized to avoid selection bias. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial [36].

7.8 Descriptive Studies

Descriptive studies are an important component of pharmacovigilance although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations [15].

7.9 Natural Disease History

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports into perspective [5].

7.10 Drug Utilization Study

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence clinical, social, and economical outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics [32]. From these studies denominator data can be developed for use in determining rates of ADRs. DUS can be used to examine the relationship between recommended and actual clinical practice. These studies help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product [34].

8. IMPLEMENTATION STATUS OF HERBAL PHARMACOVIGILANCE

Pharmacovigilance involves the assessment of risks and benefits of medicines and plays a key role in pharmacotherapeutic decision making. For several years now, herbal medicines have been increasingly consumed by patients as most of them are available as OTC medication. Like synthetic drugs, herbal medicinal products also need drug surveillance in order to identify their possible long-term risks [35]. Recently, guidelines for the safe use of herbal drugs were developed by participants attending the regional workshop on the Regulation of Herbal Medicines, organized by the WHO Regional Office for South-East Asia [27].

8.1 WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems

Safety of herbal medicine is an important public health concern. The guidelines stress upon the following:

- The importance of the process for monitoring the safety of herbal medicine within the pharmacovigilance system,
- Standard definitions of terms related to pharmacovigilance and safety monitoring of herbal medicine
- Challenges in monitoring the safety of herbal medicine
- Need for good communication for ensuring successful safety monitoring. These guidelines aim to propose to member states a framework for facilitating the regulation of herbal medicines/ products used in traditional medicine. The issues it covers are as follows:
 - Classification of herbal medicines
 - Minimum requirements for assessment of safety of herbal medicine
 - Minimum requirements for assessment of the efficacy of herbal medicines
 - Quality assurance of herbal medicinal products
 - Pharmacovigilance of herbal medicinal products and
 - Control of advertisements of herbal medicinal products

The guideline is beneficial to countries by serving as a reference to facilitate the setting up of requirements for registration and regulation of herbal medicines. The present models of pharmacovigilance and its associated tools have been developed in relation to synthetic drugs. Improvements in safety monitoring of herbal medicines may include modifications to existing methodology, patient reporting and greater consideration of pharmacogenetics and pharmacogenomics in optimizing the safety of herbal medicines [30].

- ✓ There is a lack of common standards of quality control and appropriate methods for evaluating traditional medicine to ensure the quality, safety and efficacy. In 2001, WHO developed the Global Survey Questionnaire which focused on the following:

- ✓ General review of policy and regulation of traditional herbal medicine
- ✓ Regulation of herbal medicines
- ✓ Countries need for future WHO support and guidance.

Routine pharmacovigilance should be conducted for all medicinal products, regardless of additional actions as appropriate as part of a pharmacovigilance plan. The best method to address a specific situation can vary depending on the issues to be addressed like the product, the indication and the target population. The method chosen can also depend on whether an identified risk, potential risk or missing information is the issue and whether signal detection, evaluation or safety demonstration is the main objective of further study. When choosing a method to address a safety concern a protocol should be finalized, and experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists and biostatisticians) should be consulted [19]. Study protocols should, as a minimum, include the study aims and objectives, the methods to be used, and the plan for analysis. The final study report should accurately and completely present the study objectives, methods, results, and the principal investigator's interpretation of the findings. A study report after completion, and an interim report if appropriate, should be submitted to the authorities according to the milestones within the pharmacovigilance plan [33].

Looking at the case of Indian, a pharmaceutical company holding the marketing license should have an adequate pharmacovigilance system. All the adverse reaction reports and the information about the benefit- risk analysis need to be shared with Drugs Controller General of India (DCGI). Indian drug regulation recognizes traditional herbal medicine considering it as an inclusive system but has not yet fully integrated it into all aspects of health care system like health care supply, education, training and drug regulation considering as an Inclusive system. Although the NPP encourage reporting of all suspected adverse events caused by herbal/traditional/ alternative medicines (Protocol of NPP, version 1, 2004, p 14) [29,34], the number of adverse reactions to Ayurvedic drugs reported or recorded in NPP is negligible. So, while approving herbal drugs for marketing license, adverse reactions reporting of adverse reactions to regulatory should be made mandatory for these formulations [35-37].

Marketing authorization of a drug is based on a satisfactory balance of benefits and risk within the conditions specified in the product labelling at the time of approval. The benefit-risk balance can be improved by reducing risks to patients through effective pharmacovigilance that can enable information feedback to the users of the medicines in a timely manner [20]. Once a new product is marketed new information will be generated, which can have an impact on the benefits or risks of the product. Evaluation of this information should be done as a continuing process, in consultation with regulatory authorities. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use. Pharmacovigilance Plan should be developed primarily focusing herbal products based on the written Safety Specification. Safety Specification should summaries the identified and potential risks of the product to be addressed in the plan. For products with important identified risks, important potential risks or important missing information, the pharmacovigilance plan should include additional actions designed to address these concerns [27].

8.2 The Following Steps Can Be Exercised for Implementation of an Effective Pharmacovigilance System

- Step 1: Pharmacovigilance Planning
 - Step 2: Development of notification culture
 - Step 3: Debriefing, Interaction, and Training
 - Step 4: Reporting method development
 - Step 5: Recording and coding the identity of herbal medicines
 - Step 6: Assessment of case reports
 - Step 7: Data analysis
 - Step 8: Data management
 - Step 9: Final reporting to regulatory or advisory committee
 - Step 10: Data maintenance
 - Step 11: Feedback to reporters
 - Step 12: Risk communication between reports, pharmacovigilance centres, UMC, consumer and mass media.
 - Step 13: Publication of information
- The pharmacovigilance plan should be updated regularly as important information on safety becomes available and milestones are reached [19].

8.3 Constraints Associated with Herbal Pharmacovigilance

The ingredients of herbal medicines are by nature complex mixtures and it is well

documented that concentrations of plant constituents can vary considerably depending on environmental and genetic factors. The constituents responsible for claimed therapeutic effects are frequently unknown or only partly understood [33,38]. This precludes the level of control that can routinely be achieved with synthetic drug substances in conventional pharmaceuticals. The position becomes even more difficult by the common traditional practice of using combinations of herbal ingredients forming polyherbal products. The following issues nurture the prevailing concern towards effective implementation of herbal pharmacovigilance [34,39,40-42];

- The lack of official recognition of all traditional and contemporary products and providers.
- Traditional herbal medicines not integrated into national health care systems.
- The lack of strictness in regulatory and legal mechanisms concerning standardization and quality control of herbal medicine.
- Variable manufacturing standards due to limited and/or absence of knowledge, error, or deliberate intent. The absence/limitation of quality assurance and control in manufacturing of herbal medicines which is a confounding factor in diagnosis of herbal adverse reactions.
- The informal as well as the regulated herbal manufacturing sector is not well standardized to identify and assay the ingredients present in a particular formulation which often makes it impossible to identify the drug causing adverse reaction.
- The methods to study and assess the safety issues of herbals are not yet well evolved.
- The pharmacokinetic and toxicokinetic studies are not routinely done for herbal medicines.
- The dose-response and time-response relationships are rarely measured and reported.
- Ambiguity over nomenclature due to incomplete description of source material or errors in identification and authentication.
- The lack of knowledge about the concept and importance of pharmacovigilance are not included in the traditional medicine curriculum.

- The concept and terminologies related to adverse reaction monitoring are not included in Ayurvedic curriculum.
- Self-medication of herbal medicines without prescription and medical supervision.
- There is a confounding factor that patients often use allopathic medicines along with herbals without any concern of practitioner.
- Inadequate allocation of resources for traditional herbal medicine development and capacity building.
- Lack of equitable and widespread distribution of benefits related to indigenous medicinal knowledge and products.

A modified reporting form that can better collect information on suspected herbal ADRs is desirable. The WHO has thus published such a modified template reporting form specifying general considerations to design model reporting form for suspected adverse reaction to medicines, including herbal medicines and vaccines [39]. Statistical generation of signals from the database of spontaneous reports also raises questions for herbals [11,38].

9. FUTURE PHARMACOVIGILANCE STRATEGIES

Developing countries must incorporate traditional herbal medicine into their National Health Care Systems as an integrative system. In an integrative system, traditional herbal medicine is officially recognized and incorporated into all areas of health care provision [2,22]. This signifies that traditional herbal medicine should be included in: Country's national drug policy; all herbal medicine providers and products are to be registered and regulated; traditional herbal therapies should be available at hospitals and clinics (both public and private); and treatment with traditional herbal medicine should be reimbursed under health insurance [11,40-42].

For the implementation of an effective pharmacovigilance program for herbal and traditional medicines the following strategies can be worked out:

1. The Traditional Herbal Registration holder should provide information to users about optimize safe and effective use of traditional herbal medicines. Assessing these data will help the regulatory bodies

to ascertain risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use.

2. Traditional Herbal Registration holders should provide succinct summary information together with a critical evaluation of the risk-benefit balance of the product in the light of new or changing information. This evaluation will ascertain whether further investigations and whether changes should be made to the registration and product information.
3. A standard classification and/or coding system for herbal medicines should be developed with standardized terms and definitions. Relevant research must be undertaken to explore detailed of pharmacogenetics and pharmacoepidemiology of herbal medicines. Providing research grants and emoluments will encourage education in the field of traditional herbal medicine.
4. Capacity must be strengthened to carry out monitoring of herbal medicines at national pharmacovigilance centers by training staff in relevant technical areas, ensuring access to facilities for analyzing products suspected of causing adverse reactions, providing access to reliable information.
5. A national safety monitoring program for herbal medicines should be operated with the will and the potential to react to signals emanating from reports of adverse effects of herbal medicines and to take proper regulatory measures.
6. Case reporting sources should be expanded involving all traditional medicine and complementary/alternative medicine, providers, strengthening the role of providers, involving manufacturers of herbal medicines, facilitating consumer reporting, developing systems of information exchange involving drug information, centers, poisons centers, consumer organizations and manufacturers. Strengthening communication and awareness at all levels (global, regional, national, local and community).
7. Interactive Reporting pattern should be developed for widespread reporting behaviour cultivation in the herbal users.
8. Model reporting forms should also be available on the Web containing all the template questions and queries required

for ideal reporting for herbal ADRs. This will help the general public to report the herbal related ADRs easily and conveniently.

9. Health-care professionals and providers of herbal medicines should ask patients directly, respectfully and persistently what other medicines they are taking, including prescription medicines, herbal medicines and other health products for self-care.
10. Involvement of all health-care professionals: Physicians, Surgeons, Dentists, Pharmacists, and Nurses etc in herbal pharmacovigilance will boost up the progression towards achieving the goal of safety herbals.
11. Monitoring the impact of any action taken against the reporting of ADRs are very crucial for effective implementation of pharmacovigilance system. Collaborative approach can be adopted by the manufacturer, regulatory, CDSCO and WHO for safety aspect monitoring.
12. The PSUR submission must be made compulsory for herbal products including all dosage forms and formulations, as well as all indications, associated with an active ingredient. Within the PSUR, separate presentations of data for different dosage forms, indications or populations (for example, children vs. adults) may be appropriate, however an overview of the combined data should also be provided.
13. Once a traditional herbal product is registered, even if it is not marketed, Periodic Safety Update Reports (PSURs) must be submitted. PSURs are required to be prepared at set intervals for the lifetime of that product.
14. For combinations of substances which are also registered individually, safety information for the fixed combination may be reported either in a separate PSUR or be included as a separate presentation in the PSUR for one of the separate components, depending on the circumstances. Cross referencing all relevant PSURs is essential.

10. CONCLUSION

Pharmacovigilance in traditional medicine is very important to guarantee efficacy, safety and quality of the natural product under the consumption of the population. The current model of pharmacovigilance and its associated

tools have been developed in relation to synthetic drugs, and applying these methods to monitoring the safety of herbal medicines presents unique challenges in addition to those described for conventional medicines. Several problems relate to the ways in which herbal medicines are named, perceived, sourced, and utilized. Challenges also arise from the current regulatory framework for herbal medicines in resource limited countries. Unnoticed ADRs are likely to be significant for herbal medicines, since users typically do not seek professional advice about the use of such products, or report if they experience adverse effects. Many consumers are hard to reach through the usual healthcare professional channels (eg pharmacies) as they do not obtain their products from registered/licensed drug stores. Several other tools used in pharmacovigilance of conventional medicines, such as prescription-event monitoring, and the use of computerized health-record databases, currently are of no use for evaluating the safety of herbal and other non-prescription medicines. If traditional medicines are to be promoted as a source of healthcare promoter, efforts should be made to promote its rational use and for this identification of the safest and most effective therapies will be crucial. Adulteration of herbals with pharmaceutical drugs is a problem in many countries. In the present scenario, when ADR Monitoring is being done on wide scale and in a well-maintained method, there is still a very low reporting of adverse drug reactions of herbs. The legal status and approval mechanism of herbal medicine also varies from country to country and risks associated with its irrational use are also greater.

A drug reaction monitor center for herbal drugs should be set-up by the WHO or other organizations. However, the project of the WHO Collaborating Centre for International Drug Monitoring on safety monitoring of herbal medicines is crucial. Herbal pharmacovigilance should be implemented in our herbal regulatory system and authorities should record various aspects of the single herb and/or compound herbal formulations like ADR, delayed or acute toxic effects, allergies etc. Spontaneous reporting forms are not designed to collect information on herbal medicines, and the reporter needs to be prompted for the specific information required. A modified reporting form that can better collect information on suspected herbal ADRs is desirable. Continuous evaluation of their benefit and harm will help to achieve the ultimate goal to

make safer and more effective treatment through herbal medicines available to patients. Regulatory agencies should make an effort to create awareness about the science of pharmacovigilance among herbal physicians, patients and paramedical staff.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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