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Pharmacovigilance of Herbal Drugs (Herbovigilance)

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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 a 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. The importance of herbal remedies in pharmacovigilance systems is becoming one of the primary tasks, due to the constantly ascending potential of herbal products and herbal medicines worldwide. Nowadays, the drug development is focused on finding new active compounds or combinations, but costs are simultaneously growing, which makes herbal medicines an attractive, harmless and cheaper alternative to synthetic drugs.

Like all drugs, herbal are not free of risk and many studies suggest for potential adverse reactions and interactions. Available statistics show that some herbal products, used in traditional medication for generations, may possess carcinogenic, hepatotoxic, cardiotoxic and other severe actions. Evaluation of the safety should include at least in vitro and in vivo genotoxicity assays, long-term rodent carcinogenicity tests (for drugs intended to be continuously used for >3 months or intermittently for >6 months), reproductive and developmental toxicity studies in some cases and examination of the effects on drug-metabolizing enzymes.

Drug safety of herbal medicines should be developed, focusing on specific groups of patients. Herbal formulations being widely accepted therapeutic agents as antidiabetics, antiarthritics, hepatoprotectives, cough remedies, memory enhancers, and adaptogens. The commonest myth regarding herbal medicines is that these medicines are completely safe, and can therefore be safely consumed by the patient on his/her own, without a physician's

prescription. This belief has led to large-scale self-medication by people all over the world, often leading to disappointing end-results, side-effects, or unwanted after-effects. There is an increasing awareness at several levels of the need.

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. 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. 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. 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. 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. Pharmacovigilance is a crucial tool for developing reliable data on the safety of marketed drugs under the practical conditions of clinical usage in society. The aim is to prolong safety monitoring and detect drug adverse events that have been previously unrecognised, despite evaluation in clinical trials. Although these approaches were established for monitoring pharmaceutical medicines,they are also used for assessments of the safety of other medicinal products including herbals, blood products, vaccines and medical devices. The World Health Organisation (WHO) recognised the arising importance of the consumption of herbal medicines worldwide and developed guidelines for the monitoring of herbal safety within the current pharmacovigilance framework – "WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems".The significance of herbal

medicine practices is confirmed by the fact that 67.6% of the population of United States had used herbal medicines – US$ 17 billion were spent by more than 158 million Americans in 2000. Statistics on 3027 South Australians, predicted that approximately 52.1% had declared at least one form of herbal product in the year 2000 and 23.3% of all respondents had visited at least one herbal practitioner during that year. 57.2% of herbal users did not discuss it with their physician. A recent report from Germany indicated that more than 70% of the population used "alternative medicines" and for majority, herbal medicinal products were the first choice in the treatment of minor diseases or disorders.

About 80% of the developing world's population depends on traditional medicine for their primary health care. Results obtained from studies in Nigeria show inadequate adverse effects monitoring amongst the practitioners and underscore the necessity to educate and enlighten herbal medicine practitioners on the need for pharmacovigilance activity of herbal products.

Prognoses for next years for the global herbal market are promising. New reports estimate to reach about US$100 billion by 2015,and US$107 billion by 2017.One possible reason could be related to the growing aging population. A group of the first Baby Boomers are turning 65 this year and they are a major consumer group of herbal drugs and supplements, particularly women in the middle-age.Negative opinions about herbal ingredients (such as ephedra) have been reduced. The reports note a "major tendency" in the herbal market as the shift from single ingredient preparations to the largest segment "multiple ingredient-based medications" is constantly rising – 20% of adult patients are using a dietary supplement with at least one herbal ingredient. The market for homeopathic and herbal remedies continues to grow, and it was estimated to increase 2.6% from 2011–12. According to reports from Global Industry Analysts, Europe is the primary herbal market that shares 45% of total, next is North America with 11%, Japan 16%, ASEAN countries 19% and the remaining with 4.1%. Market with the highest growth rate is Asia-Pacific with CAGR (Compound Annual Growth Rate) of 10.7% through 2015.Countries like Japan and China have successfully marketed their traditional medicines abroad. Sales of herbal dietary supplements in the United States increased by 7.9% in 2013, reaching a total estimated figure of six billion dollars for the first time. The total sales figure of US$994,228,073 for botanical dietary supplements in 2013 is the reflex of an increase of 9.4% compared to 2012.The systematic evaluation of safety and efficacy of herbal products and preparations is thus of vital importance from both medicinal and economic perspectives.About two centuries ago, health care system was dominated by natural materials derived from plants,animals and minerals. The medicine traditions were developed over generations and had been mostly transmitted orally by local herbal medicine practitioners. Numerous aspects of Ethnomedicine systems from many cultures – Ayurveda, Siddha and Unani medicine from the Middle East and South Asia, Kampo medicine from Japan, Traditional Chinese Medicine (TCM), Muti from Southern Africa, West Africa, Islamic medicine – have been well documented and could be an enormous potential for the development of novel agents.

The end of World War II initiated the rapid development of advanced chemical technologies. Majority of natural products declined its use in the West when more predictable synthetic drugs were made commonly available. However, about 25% of drugs currently used owe their active properties to plants as isolates or modified

isolates, like it was with aspirin, as synthetic compounds.

Atropa Belladonna, Papaver Somniferum, Digitalis Purpurea and Hypericumperforat um are examples of plants that have strong position in present treatments.

Since around 30 years, popularity of herbs and traditional medicine is again increasing steadily. Supportive was a fact, that many medicinal herbs started being sold in drug-like forms such as capsules, tablets, covered-tablets, and pastilles, which may be more attractive or tasty for consumers. These concentrated formulations made application easier to dose regularly in high concentrations. It is estimated that 40,000–70,000 plant species are used currently as medicines. The World Health Organization (WHO) admitted the widely usage of plants in the early 1970s and started supporting governments to effectively use local knowledge of herbal medicines for disease prevention and health campaign. However, herbal medicines have many weaknesses. These include insufficient and unacceptable requirements for safety, efficacy, standardization, and inconsistent production practices. In the Ipsos MORI report published in November 2008, 77% of British adults agreed with support and need for regulation of herbal medicines. Modern medicines are relatively more focused on particular diseases, based on specific etiopathological entities. Many of current plaguing humanity diseases are multifactorial, e.g. cancer, so the rational becomes the research of multi-target drugs. Screening of medicinal plants as a source of antitumor agents started in the middle of last century, with the isolation of vinca alkaloids-vinblastine and vincristine. More than 60% of cancer therapeutics registered on the market or under testing is based on natural products. The choice of the patient to use drugs with plant origin may be caused by several factors, involving poor accessibility to modern drugs, high costs, shortage of physicians, over the counter availability, opinion that natural is absolutely safe, more a adverse effects reported with modern medicine than for herbal preparation, placebo effect, cultural and religious beliefs, educational level, lack of effective treatments, peer

influence, etc. Obstacles to use of herbal medicines may be: potential for interactions, difficulties to identify ingredients, less knowledge of adverse reactions of herbal drugs and lack of good manufacture practices.

Traditional medical knowledge, often called complementary or alternative medicine, has two potential values – one as an easy accessible and low-cost source of medicines for primary health care and other as the source for finding novel leads and/or targets for drug development.

Objective

- To create a nation-wide system for patient safety reporting.
- To identify and analyze the new signal (ADR) from the reported cases.
- To analyses the benefit - risk ratio of marketed medications.
- To generate the evidence based information on safety of medicines.
- To support regulatory agencies in the Decision-making process on use of medications.
- To communicate the safety information on use of medicines to various stakeholders to minimize the risk.
- To emerge as a national center of excellence for pharmacovigilance activities.
- To collaborate with other national centers for the exchange of information and data management.
- To provide training and consultancy support to other national pharmacovigilance centers located across globe.

Aim of Pharmacovigilance Programme of India:

PV has specific aims as follows:

1. Improve patient care and safety in relation to the use of medicines and all medical and

paramedical interventions

2. Improve public health and safety in relation to the use of medicines

3. Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging

their safe, rational and more effective (including cost effective) use

4. Promote understanding, education and clinical training in PV and its effective communication

to the public.

Role of Pharmacovigilance Programme of India:

PvPI is a flagship program under the aegis of MoHFW; GOI is working with the sole conviction to identify, monitor, prevent adverse drug reactions (ADR) associated with medications prescribed in India, and to promote patient safety. The main objective of the PvPI is to identify signals and to minimize the risk associated with the use of medications in the public of India.

At present, 250 ADR monitoring centers (AMCs) are working under the umbrella of PvPI to monitor and report ADRs to NCC-PvPI. The program is steered from IPC, Ghaziabad. These AMCs cover government and private teaching hospitals, corporate hospitals, specialized hospitals, government general hospitals, TB and HIV treatment center etc.

Capacity building, strengthening legislation, and stakeholder coordination/cooperation are the crucial force behind the development of pharmacovigilance. NCC-PvPI, IPC is the apex body for creating awareness, and strengthening the pharmacovigilance has taken many steps. One such landmark achievement is the commencement of Skill Development Program on "Basics and Regulatory Aspects of Pharmacovigilance" to enhance the skills of the workforce engaged in pharmaceutical industry and to effectively meet quality standards.

PvPI works closely with AMCs, Indian Council of Medical Research, IMA and has

harnessed their potential in creating awareness on reporting of ADRs and prudent use of antibiotics. Now, with the advent of a more difficult problem of AMR as a patient safety concern, the NCC has taken pledge to sensitize all the stakeholders in this regard. Following initiatives have been taken by NCC-PvPI to prevent the occurrence of AMR in Indian population

Scope of Pharmacovigilance Programme of India:

Before registration and selling of drugs within the country, its safety and efficaciousness expertise area unit primarily based totally on the employment of the drugs in clinical trials.

These trials in the main notice common ADR. Some vital reactions, like those, that take a protracted time to develop, or those, that occur seldom, might not be detected in clinical trials.

Additionally, the controlled conditions beneath that medicines area unit utilized in clinical trials don't essentially replicate the method they will be utilized in observe. For a drug to be thought-about safe, its expected advantages ought to be more than any associated risks of harmful reactions. So, so as to achieve a comprehensive safety profile of drugs, a continuous post-marketing monitoring system i.e. PV is crucial. So as to monitor the security of drugs, information from several sources is employed for PV.

These embrace spontaneous ADRs coverage mechanism; medical literature published worldwide; action taken by regulative authorities in alternative countries. Since there exist substantial social and economic consequences of ADRs and therefore the positive benefit/cost magnitude relation of implementing applicable risk management -there may be a have to be compelled to interact health care professionals and therefore the public at massive, during a well-structured programme to make synergies for watching ADRs within the country.

The aim of the PvPI is to collate data, method and analyse it and use the inferences to advocate regulative interventions, besides human action risks to health care professionals and therefore the public.

Pharmacovigilance Programme Of India :

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in association with Indian Pharmacopeia commission, Ghaziabad is initiating a nation-wide Pharmacovigilance Programme for protecting the health of the patients by promising drug safety. The Programme shall be coordinated by the Indian Pharmacopeia commission, Ghaziabad as a National Coordinating Centre (NCC). The center will operate under the supervision of a Steering Committee.

The Pharmacovigilance Programme of India (PvPI) was started by the Government of India on 14th July 2010 with the All India Institute of Medical Sciences (AIIMS), New Delhi as the National Coordination Centre for monitoring Adverse Drug Reactions (ADRs) in the country for safe-guarding Public Health. In the year 2010, 22 ADR monitoring centres including AIIMS, New Delhi was set up under this Programme. To safeguard implementation of this programme in a more effective way, the National Coordination Centre was shifted from the All India Institute of Medical Sciences (AIIMS), New Delhi to the Indian Pharmacopoeia Commission, Ghaziabad,

Uttar Pradesh on 15th April 2011.Before registration and marketing of medicine in the country, its safety and efficacy experience is based chiefly on the use of the medicine in clinical trials. These trials primarily detect common adverse reactions. Some important reactions, such as those, which take a long time to develop, or those, which occur rarely, may not be detected in clinical trials. In addition, the controlled conditions under which medicines are used in clinical trials do not necessarily reflect the way they will be used in practice. For a medicine to be considered safe, its predictable benefits should be greater than any associated risks of harmful reactions. So, in order to gain a complete safety profile of medicine, a continuous post-marketing monitoring system i.e. pharmacovigilance is essential. In order to screen the safety of medicine, information from many sources is used for pharmacovigilance. These include spontaneous (ADRs) reporting mechanism; medical literature published worldwide, action taken by regulatory authorities in other countries, etc. Meanwhile there exist considerable social and economic consequences of adverse drug reactions and the positive benefit/cost ratio of employing appropriate risk management (there is a need to engage healthcare professionals and the public at large, in a well-structured programme to build synergies for monitoring adverse drug reactions in the country). The purpose of the PvPI is to collate data, process and analyze it and use the inferences to recommend regulatory interventions, besides communicating risks to healthcare professionals and the public.

Mission: Safeguard the health of the Indian population by ensuring that the benefits of use of medicine outweigh the risks associated with its use.

Vision: To improve patient safety and welfare in Indian population by monitoring the drug safety and thereby reducing the risk associated with use of medicines.

Reporting and Drug Adverse Reactions:

Suspected ADR reporting forms for health care professionals and for consumers are unit available on the website of IPC to report ADR. To get rid of barrier in ADR reporting, the consumer reporting form are available in 10 vernacular languages(Hindi, Tamil, Telugu, Kannada, Bengali, Gujarati, Assamese, Marathi, Oriya, and Malayalam). ADRs will be conjointly reportable via PvPI helpline number (1800-180-3024) on week days from 9:00 am to 5:30 pm. The mobile Android application for ADR reporting has conjointly been created available to the general public.

Whom to Report:

A reporter can send filled ADR reporting form directly to NCC or their nearest AMC. In case of AMC, these reports are confirmed by healthcare professionals and entered into Vigiflow and sent to NCC for further assessment. These reports are then finally reviewed at NCC and committed to WHO-Uppsala Monitoring Centre. The obtained information is entered in the drug safety database, analyzed, and assessed by the experts to identify new signals. The submitted ADR report does not have any legal implication on the reporters. The patients' identity are held in strict confidence and protected to the fullest extent.

Therefore, healthcare providers are encouraged to report ADRs for better understanding of the risk associated with the use of medicines and to safeguard the health of Indian population.

Where to Report:

All healthcare professionals (clinicians, dentists, pharmacists, nurses) and NCC patient/consumers can report ADRs to NCC or AMCs. The pharmaceutical companies can also send individual case safety reports for their product to NCC.

What to Report:

PvPI encourages all types of suspected ADRs reporting whether they are known, unknown, serious, or nonserious, frequent, or rare regardless of an established causal relationship between a drug and the reaction. ADRs related with the use of allopathic medicines, vaccines, traditional medicines, medical devices, contrast media, etc., can be reported.

Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION
(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

FOR AMC/NCC USE ONLY

AMC Report No. :

Report Type ☐ Initial ☐ Follow up

Worldwide Unique No. :

A. PATIENT INFORMATION

1. Patient Initials _____
2. Age at time of Event or Date of Birth _____
3. M ☐ F ☐ Other ☐
4. Weight_____Kgs

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)
6. Date of recovery (dd/mm/yyyy)
7. Describe reaction or problem

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)

14. Seriousness of the reaction: No ☐ if Yes ☐ (please tick anyone)
☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly
☐ Life threatening ☐ Required intervention to Prevent permanent
☐ Hospitalization/Prolonged impairment/damage
☐ Disability ☐ Other (specify)

15. Outcomes
☐ Recovered ☐ Recovering ☐ Not recovered
☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates		Indication	Causality Assessment
								Date started	Date stopped		
i											
ii											
iii											
Iv											

S.No as per C	9. Action Taken (please tick)						10. Reaction reappeared after reintroduction (please tick)			
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates		Indication
					Date started	Date stopped	
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS

16. Name and Professional Address:_____
_____
Pin:_____E-mail_____
Tel. No. (with STD code)_____
Occupation:_____ Signature:_____

17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

Table No:- 1.1 ADRs Reporting Form

Chapter:- 2

Literature Review

1. **Sandeep Shetti et al., (2011):** Currently, a majority of the adverse events related to the use of herbal products and herbal medicines that are reported are attributable either to poor product quality or to improper use. Inadequate regulatory measures, weak quality control systems, and largely uncontrolled distribution channels (including mail order and Internet sales) may have been contributing to the occurrence of such events. In order to expand the knowledge about genuine adverse reactions to herbal medicines, and to avoid wasting scarce resources for identifying and analyzing adverse events, events resulting from such situations will need to be reduced or eliminated. Member States of the World Health Organization (WHO) are therefore encouraged to strengthen

national regulation, registration and quality assurance and control of herbal medicines. In addition, the national health authorities should give greater attention to consumer education and to qualified practice in the provision of herbal medicines.

2. **Raja Chakraverty et al., (2019):** Pharmacovigilance (PV) activities have indeed come a long way in India since the inception of national policy facilitating the transition from the erstwhile National Pharmacovigilance Program to ushering the genesis of the Pharmacovigilance program of India (PVPI) back in 2010. Broadly, this science and practice encompass-es activities related to the detection, assessment, understanding and prevention of adverse drug reactions (ADR) or any other pos-sible drug-related problems including the much neglected case of herb-drug interactions. In the recent past, however, its purview has been widened to include herbal, traditional and complementary medicines (AyUSH) with the goal to comprehensively detect, assess, and understand adverse reactions from herbal products with the unanimous goal of preventing occurrence of adverse effects among end-users. The established methods for conducting herbovigilance is similar to PV and includes but are not limited to-spontaneous reporting, cohort report monitoring and targeted spontaneous reporting from adverse drug monitoring centres (AMC) scattered all across over this nation and collated and analysed at the CDSCO, Ghaziabad and ultimately at the Uppsala Monitoring Centre (WHO-UMC) based in Sweden. Signal detection and causality assessment of reports generated from herbal products assume a great signifi-cance owing to its use by a large proportion of fellow citizens in both rural and urban demography and thus its role in reporting of rare herbal medicine induced disorders that often goes unnoticed.

The literature search conducted presenting this commentary was based on extensive topic related search of contemporary scientific articles and complementary review of bibliographies from selected publications on the subject of Herbovigilance and its chronological evolution till date. The promotion of systematic and rational use of drugs and shift of the paradigm from drug safety to patient safety requires the reporting of adverse events possibly caused by herbal and traditional medicines with their mechanistic underpinnings. Proper reporting of suspected adverse drug reactions from herbal medicine practitioners in Ayurveda, siddha and other Ayush disciplines has, therefore, assumed a greater role in the holistic outlook of therapeutics of today and requires proper and careful vetting prior to guideline based implementation from stakeholders in the healthcare sector (practitioners, pharmacists and nurses). Thus, in summary this editorial attempts to stress on the need for nurturing our national herbovigilance activities and creation of many more resource centres which is quite essential to build up reliable information database much like Vigibase based on data from the Indian network regarding the safety of herbal medicines to boost confidence about their safety making it at par with the system of mod-ern medicine in terms of the credible evidence available in public and legislative domains.

3. **Kamila Gromek et al., (2015):** The importance of herbal remedies in pharmacovigilance systems is becoming one of the primary tasks, due to the constantly ascending potential of herbal products and herbal medicines worldwide. Nowadays, the drug development is focused on finding new active compounds or combinations, but costs are simultaneously growing,

which makes herbal medicines an attractive, harmless and cheaper alternative to synthetic drugs. Like all drugs, herbal are not free of risk and many studies suggest for potential adverse reactions and interactions. Available statistics show that some herbal products, used in traditional medication for generations, may possess carcinogenic, hepatotoxic, cardiotoxic and other severe actions. Evaluation of the safety should include at least in vitro and in vivo genotoxicity assays, long-term rodent carcinogenicity tests (for drugs intended to be continuously used for >3 months or intermittently for >6 months), reproductive and developmental toxicity studies in some cases and examination of the effects on drug-metabolizing enzymes. Drug safety of herbal medicines should be developed, focusing on specific groups of patients.

4. **Gaurav Ranjan et al., (2021):** With increase in popularity and use of herbal products both as medicine and nutraceuticals throughout the world, there is an urgent need to monitor their adverse drug reactions. Pharmacovigilance is the discipline of monitoring, reporting and evaluating adverse drug reaction for medicinal products including herbal medicines. However, the current model of pharmacovigilance, its activities and associated tools have been developed with respect to conventional medicines. Applying these methods to monitor the safety of herbal medicinal products provides new challenges due to the diverse nature, regulatory requirements and usage of these products. In this chapter we discuss the importance and regulations associated with monitoring adverse drug reactions of herbal medicine. We also discuss the current challenges and future opportunities in this evolving field of importance.
5. **Eliana Rodrigues et al., (2012):** Typically, ethnobotanical/ethnopharmacological (EB/EP) surveys are used to describe uses, doses/dosages, sources and methods of preparation of traditional herbal medicines; their application to date in examining the adverse effects, contraindications and other safety aspects of these preparations is limited. From a pharmacovigilance perspective, numerous challenges exist in applying its existing methods to studying the safety profile of herbal medicines, particularly where used by indigenous cultures. This paper aims to contribute to the methodological aspects of EB/EP field work, and to extend the reach of pharmacovigilance, by proposing a tool comprising a list of questions that could be applied during interview and observational studies. The questions focus on the collection of information on the safety profile of traditional herbal medicines as it is embedded in traditional knowledge, as well as on identifying personal experiences (spontaneous reports) of adverse or undesirable effects associated with the use of traditional herbal medicines. Questions on the precise composition of traditional prescriptions or 'recipes', their preparation, storage, administration and dosing are also included. Strengths and limitations of the tool are discussed. From this interweaving of EB/EP and pharmacovigilance arises a concept of ethno pharmacovigilance for traditional herbal medicines: the scope of EB/EP is extended to include exploration of the potential harmful effects of medicinal plants, and the incorporation of pharmacovigilance questions into EB/EP studies provides a new opportunity for collection of 'general' traditional knowledge on the safety of traditional herbal medicines and, importantly, a conduit for collection of spontaneous reports of

suspected adverse effects. Whether the proposed tool can yield data sufficiently rich and of an appropriate quality for application of EB/EP (e.g. data verification and quantitative analysis tools) and pharmacovigilance techniques (e.g. causality assessment and data mining) requires field testing.

6. **P. Nainwal et al., (2010):** Herbal medicines make up an important module of the fashion toward alternative medicine. It is becoming ever more popular in today's world as people seek out for natural remedies. These medicines have been used since the dawn of civilization to maintain health and to treat various diseases. To compete with the growing pharmaceutical market, there is an exigency to develop and scientifically validated more medicinally useful herbal products. This review provides an outline of herbal medicines which is aimed to depict out pharmacovigilance, including standardization of these herbal products**.**
7. **Archana V. Rajdeo et al., (2018):** Ayurvedic medicines are used since ancient times. Herbal formulations being widely accepted therapeutic agents as antidiabetics, antiarthritics, hepatoprotectives, cough remedies, memory enhancers, and adaptogens. The purpose of pharmacovigilance is to detect, assess, and understand, and to prevent the adverse effects or any other possible drug-related problems, related to herbal, traditional, and complementary medicines. The objective of the present article is to review the recent trends and challenges posed in the practice of pharmacovigilance of herbal drugs. An Adverse Reaction is defined as a noxious and unintended response to a marketed health product, which occurs at doses normally used or tested for the diagnosis, treatment, or prevention of a disease or the modification of an organic function. Adverse events may also arise from the misuse of the wrong species of medicinal plants, incorrect dosing, errors in the use of herbal medicines by healthcare providers and consumers, interactions with other medicines, and use of products contaminated with potentially hazardous substances, such as toxic metals, pathogenic microorganisms, and agrochemical residues. The availability of herbal products as "over-the- counter" drugs and their increasing use since these products are not currently monitored for their safety, efficacy, and quality. It has now become evident, that there is need for a holistic approach to the health care.
8. **Kumud Upadhyaya et al., (2017**): A recent report suggests global market for medicinal plants is around $60 billion growing at a brisk pace of seven to eleven percent annually. Out of the annual consumption of raw drugs, 50 per cent are from roots, 15 per cent from fruits/seeds, 12 per cent from wood, 9 per cent from whole plants, 7 per cent from bark/stem, 4 per cent from leaves and 3 per cent from flowers. Termed as CAM (Complimentary and Alternative Medicine) herbal medicine have long been considered safe alternative for modern medicine. Recent development in research in herbal medicine has necessitated the efforts to further explore safety aspects of Herbal medicine. Pharmacovigilance of herbal medicine is now an issue to be given ample attention. FDA across the word has tightened their noose on safety issues of herbal medicine
9. **S.K et al., (2014)**: There is popular misconception that natural means safe and remedies of natural origin are harmless and are devoid of adverse drug reactions (ADRs). "Charka Samheta", classical book of Ayurveda describes adverse drug reaction

(ADRs) when herbal medicines are used or prepared inappropriately. As per WHO guidelines, most of the ADRs linked with herbs and herbal products are because of poor product quality or improper usage. There may be adulteration with toxic metals, potent drugs and agro chemicals etc. Besides there may be presence of pathogenic micro-organisms if appropriate measures are not taken in herbal drug products. WHO further declares that there are inadequate regulatory measures, weak quality control and largely uncontrolled distribution channel for herbal products. National surveillance system to monitor and evaluate ADRs with herbal medicines is rare. Since there is continuous increase in usage and demand for herbal product, it is required to strengthen the national regulation, registration, quality assurance and control of herbal medicines. One should never forget these words of Charka "even a strong poison can become an excellent medicine if administered properly and on the other hand even the more useful drug can act like a poison if handled carelessly". This paper deals with regulatory aspects and quality control measures to be followed for herbal drug products.

10. **Shaw Debbie et al., (2012):** Pharmacovigilance is essential for developing reliable information on the safety of herbal medicines as used in Europe and the US. The existing systems were developed for synthetic medicines and require some modification to address the specific differences of medicinal herbs. Traditional medicine from many different cultures is used in Europe and the US which adds to the complexities and difficulties of even basic questions such as herb naming systems and chemical variability. Allied to this also is the perception that '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. Cooperation between orthodox physicians and traditional practitioners is needed to bring together the full case details. Independent scientific assistance on toxicological investigation, botanical verification can be invaluable for full evaluation of any case report. Systematic pharmacovigilance is essential to build up reliable information on the safety of herbal medicines for the development of appropriate guidelines for safe effective use.

Chapter:-3

Aims & Objectives

Aim & Objective of Pharmacovigilance of Herbal Drugs:

The study has been done on the basis of secondary data collected from internet search and literature survey, analyzed the data of national drug regulatory authority, world health organization and the survey of clinical practice of pharmacovigilance.

- Introduce pharmacovigilance concepts into the curriculum of herbals at the undergraduate and postgraduate level.
- Make reporting of adverse reactions to regulatory mandatory for herbal formulations.
- Human resource development is a key feature for the success of this enterprise. It will be necessary to train herbal experts in the science of pharmacovigilance and include them not only in reporting but also in assessment of the adverse reactions.
- Healthcare professionals should remain vigilant for potential interactions between herbals and prescription medications, especially when it involves medications with narrow

therapeutic indices. Due to the wide use and easy availability of herbal medicines, herbal toxicity has become an issue of concern. The safety and quality of herbal medicine should be ensured through greater research, pharmacovigilance, greater regulatory control, and better communication between patients and health professionals. The recommended approach is to include herbal medicines in existing national pharmacovigilance systems or, where such systems have not yet been developed, to establish comprehensive national pharmacovigilance systems which incorporate coverage of herbal medicines. Pharmacovigilance in herbal medicine in India is perhaps an unthought of concept as yet; we do not need "Herbal thalidomide" to wake the pharmacovigilance community to the need of the hour.

Methodology of Pharmacovigilance of Herbal Drugs:

1. Literature survey on the basis of ethnomedicinal or folklore observations.

2. Study of plants parts used.

a) Pharmacognostic Investigations

- Collection and authentication.
- Organoleptic evaluation.
- Physicochemical evaluation.

b) Phytochemical Investigations.

- Extraction in different solvents
- Preliminary qualitative chemical analysis.
- Separation and isolation of active phytoconstituents of active extracts
- Characterization of active phytoconstituents

3. Pharmacological Screening

- In-vivo or in-vitro studies of various formulations of active extracts of the selected plants

Limitation of Study

The report an investigation about Pharmacovigilance is mainly based on the secondary data collected from various sources.

Herbal medicines can treat minor conditions like scrapes, rashes and burns. They can also be used to treat migraines, arthritis and depression (University of New Hampshire) at a very low cost. The cost of herbal medicines are very low compared to pharmaceutical drugs because they can be found in local supermarkets or grown at home. According to Christopher Golden from Harvard University Center for the Environment, if people used herbal medicines in place of pharmaceuticals, they could save themselves 22-63% of what they spend on healthcare annually. Herbal medicine can also be found in everyday foods such as ginger, garlic and rhubarb.

Herbal medicines are often self administered. As a result, there is no dosage or warnings specified. When Herbal medicines are consumed with pharmaceutical drugs, the two can interact with each other resulting in injuries to health. It is also important to know that plants used as a herbal medicine may poison rather than cure someone. It may be the case where a certain part of a plant may be edible and another part may be poisonous. Take rhubarb for example. The roots of rhubarb is used as a laxative and the stem is edible. However, its leaves are poisonous. An individual may not be able to identify a poisonous plant. This would put the individual at the risk of poisoning themselves or others.

Today, people around the globe are giving preference to alternative medicines such as ayurveda, naturopathy, homeopathy and herbal medicine. It is worth mentioning that these natural and alternative medicines were used thousands of years ago. Archaeological evidences reveal that the

civilizations of the bygone era used herbal plants as part of traditional medicine. The earliest documentation about the usage of herbal remedies comes from China and dates back to 2800 BC. For almost 5000 years, herbal medicine was used for treating various ailments. Today, it has been developed as a separate industry as many people favor herbal medicine over synthetic medicine.

Chapter:-4

Current Scenario:

Today estimate that about 80% of people in developing countries still relays on traditional medicine based largely on species of plants and animals for their primary health care. India has one of the richest plant traditions in the world. These are estimated to by around 25,000 effect plant based formulations, used in folk medicine and known to rural communities in India. India's share in the export of herbals is USD 63 billion which is just 0.2% of the global herbal market. So there is obviously vast scope for Indian manufacturers for entering the growing worldwide opportunity of business in herbal pharmaceutical field. We also have to focus on standardization of herbal products. Pharmaceutical export promotion council i.e PHARMEXCIL is ready to play a key role in this regards. Currently, a majority of the adverse events related to the use of herbal products and herbal medicines that are reported are attributable either to poor product quality or to improper use. Inadequate regulatory measures, weak quality control systems and largely uncontrolled distribution channels may have been contribution to the occurrence of such events. So Pharmacovigilance of herbal medicines is required.

India has one of the richest plant traditions in the world. These are estimated to by around 25,000 effect plant based formulations, used in folk medicine and known to rural communities in India. These are over 1.5 million practioners of traditional medicinal system using medicinal plants in preventive, promotional and curative applications. It is estimated that there are over 7800 medicinal drug manufacturing units in India, which consume about 2000 tones of herbs annually. During 1950-1970 approximately 100 plants based new drugs were introduced in the usa drug market including reserpidine, rescinnamine, reserpine, vinblastine and vincristine which are derived from higher plants. From 1971-1990 new drugs such as etoposide, E-guggulsterone, artemisinin and ginkolides appeared all over the world. Plant base drugs provide outstanding contribution to modern therapeutics for example serpentine isolated from the root of Indian plant Rauwolfia serpentine in 1953, was a revolutionary event in the treatment of hypertension and lowering blood pressure. Vinblastine isolated from Catharanthus roseus is used for the treatment of hodgkins, choriocarcinoma, non-hodgkins lymphomas, leukemia in children, testicular and neck cancer. Vincristine is recommended for acute lymphocytic leukemia. Podophyllum emodi currently used against testicular small cell lung cancer and lymphomas. More than 64 plants have been found to possess significant anti-bacterial properties and more than 24 plants have been found to possess anti-diabetic properties. Teniposide and etoposide isolated from podophyllum species are used for testicular and lung cancer. Taxol isolated from Taxus brevifolius is used for the treatment of metastatic ovarian cancer and lung cancer.

Market value of Herbal Medicine:

India's share in the export of herbals is USD 63 billion which is just 0.2% of the global herbal market. So there is obviously vast scope for Indian manufacturers for entering the growing worldwide opportunity of business in herbal pharmaceutical field. In many countries

our product can be registered and thus can gain the necessary reliability for their export. The registration guidelines for every country are different and unique hence a thought should also be given to the possibility of melting such requirements before identification of market for our product. Global awareness for quality is high and we must emphasize on quality building into the product. The manufacturing facilities and infrastructure should comply with the GMP standards. Our own drugs and cosmetics law & rules define GMP for traditional medicinal products, in schedule T and every effort should be made by each and every manufacturer so as to comply with these standards.

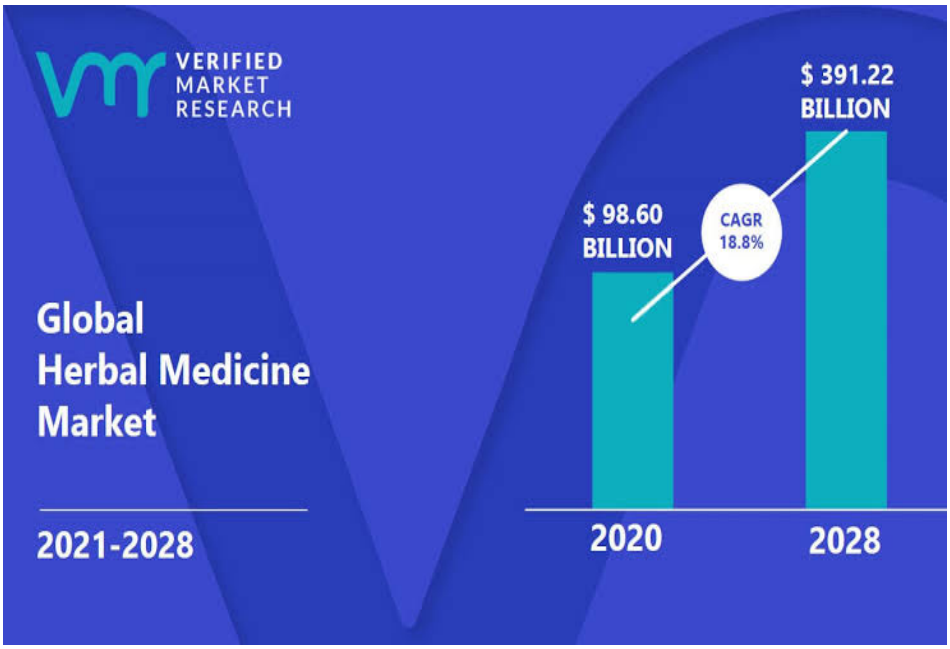

Table:- 4.1 Global Herbal Medicine Market Growth (2021-2028)

Chapter:-5

Methods in Pharmacovigilance:

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.

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. 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. 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.

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.

Stimulated Reporting:

Stimulated reporting is used to encourage and facilitate reporting of adverse events based on predesigned 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).

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.

Pharmacovigilance Sentinel Sites:

Reviewing medical records or interviewing patients or physicians in a sample of entire 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. 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.

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**.**

Registries:

A registry is a list of patients presenting with the same characteristic. 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. 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.

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).

Cross-Sectional Study:

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 trendsover 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.

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. 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.

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. How ever, 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.

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. 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.

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.

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.

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. Recently, guidelines for the safe use of herbal drugs were developed by participant attending

the regional workshop on the Regulation of Herbal Medicines, organized by the WHO Regional Office for South-East Asia.

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.
- 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. 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. 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,) 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.

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. 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.

Chapter:- 6

Future Aspects of Herbovigilance:

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. 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. For the implementation of an effective pharmacovigilance program for herbal and traditional medicines

the following strategies can be worked out:

- 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.
- 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.

- 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.
- 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.
- 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.
- 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).
- Interactive Reporting pattern should be developed for widespread reporting behaviour cultivation in the herbal users.
- Model reporting forms should also be available on the Web containing all the template questions and quarries required for ideal reporting for herbal ADRs. This will help the general public to report the herbal related ADRs easily and conveniently.
- 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.
- 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.
- 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.
- 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.
- 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.

- 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.

Consideration:

Herbal products are considered dietary supplements from a regulatory point of view. If we apply the basic principles of pharmacology to herbal medicines they can be classified into three groups: 1) Products whose efficacy has been demonstrated: their active principles are known and the therapeutic doses are established.

2) Herbal products whose efficacy is probable, but not clearly demonstrated: they contain pharmacologically active substances that are used to standardize the products. Their therapeutic dose is difficult to establish.

3) Products with uncertain efficacy but with a long-lasting traditional use: they can be useful for treating minor disorders, but should be employed exactly as in the traditional medicine. Most of the herbal products at present classified as herbal supplements fall into the second and third group: it is apparent that they cannot be considered herbal supplements.

Chapter: - 7

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.

Table of Abbreviation

WHO	World Health Organization
PHV	PHARMACOVIGILANCE
CDRA	Cameroonian Drug Regulation Agency
ADRs	Adverse Drug Reactions
NPP	National Pharmacovigilance Program
UMC	Uppsala Monitoring Centre
NPAC	National Pharmacovigilance Advisory Committee
PSURs	Periodic Safety Update Reports
OTC	OVER THE COUNTER
DSHEA	Dietary Supplement Health and Education Act
EPPV	Early Post- marketing Phase Vigilance
TCM	Traditional Chinese Medicine
CAGR	Compound Annual Growth Rate
HPLC	High-performance liquid chromatography
EB	Ethnobotanical

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Annexure:

Version-1.2

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION
(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

FOR AMC/NCC USE ONLY

AMC Report No. :

Report Type ☐ Initial ☐ Follow up

Worldwide Unique No. :

A. PATIENT INFORMATION

1. Patient Initials _____

2. Age at time of Event or Date of Birth _____

3. M ☐ F ☐ Other ☐

4. Weight_____Kgs

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)

14. Seriousness of the reaction: No ☐ if Yes ☐ (please tick anyone)

☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly
☐ Life threatening ☐ Required intervention to Prevent permanent
☐ Hospitalization/Prolonged impairment/damage
☐ Disability ☐ Other (specify)

15. Outcomes

☐ Recovered ☐ Recovering ☐ Not recovered
☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

S.No	8. Name (Brand/Generic)	Manufacturer (if known)	Batch No. / Lot No.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates		Indication	Causality Assessment
								Date started	Date stopped		
i											
ii											
iii											
Iv											

S.No as per C	9. Action Taken (please tick)						10. Reaction reappeared after reintroduction (please tick)			
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	Yes	No	Effect unknown	Dose (if reintroduced)
i										
ii										
iii										
iv										

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

S.No	Name (Brand/Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates		Indication
					Date started	Date stopped	
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS

16. Name and Professional Address:_____
_____
Pin:_____E-mail_____
Tel. No. (with STD code)_____
Occupation:_____ Signature:_____

17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.