Pharmacovigilance of Herbal Medicines

S. Merlin[1], Dr. S. Swaranalatha[2], M. Suganya[3]
[1, 2, 3] Dept of pharmacology
[1, 2, 3] Pallavan Pharmacy College,Kolivakkam, Iyyengarkkulam, Kanchipuram-631502.

Abstract- *Pharmacovigilance's goal is to identify, evaluate, and comprehend any negative effects or other potential drug-related issues associated with herbal, conventional, and complementary medicines in order to prevent them. Worldwide, herbal preparations are now widely accepted as effective treatments for conditions such as diabetes, arthritic pain, liver disease, cough and cold, memory improvement, and immune stimulation. Herbs are generally thought to be safe, and more people are consuming them without a prescription.Due to a number of complex issues, such as products with multiple ingredients, poor standardisation, a lack of clinical trials, variation in manufacturing processes, contamination, adulteration, and misidentification of herbs, for example, systematic data on the incidence of adverse effects associated with traditional medicine are not yet available. As a condition for global harmonisation, the World Health Organization has established specific guidelines for the evaluation of the quality, safety, and efficacy of herbal medicines.The UK's Medicines and Healthcare products Regulatory Agency has established a "yellow card" system for reporting adverse drug reactions in order to track the security of herbal medications. This review aims to offer a thorough and critical overview of the state of pharmacovigilance for herbal medications at the local, national, and international levels. This article examines the complex issues surrounding herbal pharmacovigilance while taking into account recent developments and offers suggestions to enhance safety monitoring in the future.*

Keywords- pharmacovigilance, herbal medicines, adverse reactions, safety and efficacy.

I. INTRODUCTION

Pharmacovigilance is the science and activities concerned with the detection, assessment, comprehension, and prevention of adverse drug effects or other possible drug-related problems.Its concerns have recently expanded to include herbals, traditional and complementary medicines, blood products, and biological products.[1],[2]

Herbs have been used as medicine for as long as history has existed.According to some authors, the first recorded use of herbs for medical treatment occurred over 4000 years ago.[3] This type of medical treatment originated in China and India.Traditional Chinese medicine focuses on the interactions betweenthe body and its surroundings.A combination of treatments is then recommended, including herbs, acupuncture, and massage.

Traditional Indian medicine has been practised since 3000 BC.Ayurvedic medicine is one type of traditional Indian medicine.Herbal therapy began more recently in the United States, with the country's founding. The use of herbs today is influenced by a combination of European, Chinese, Ayurvedic, and other unconventional treatments.Medicinal plants play an important role and form the foundation of almost all traditional medical systems.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 can all result in adverse events.

The examples below show the variety of issues that can arise when using herbal medicines and products.[1]

After some patients experienced corticosteroid-like side effects, some herbal products were discovered to contain 0.1 to 0.3 mg of betamethasone per capsule.

Plant materials containing aristolochic acid were used for manufacturing herbal products due to misidentification of

medicinal plant species, resulting in severe kidney failure in patients in several countries.

Drug safety monitoring organisations have received reports of prolonged prothrombin times, increased coagulation time, subcutaneous hematomas, and intracranial haemorrhage associated with the use of Ginkgo biloba.

When used in conjunction with interferon, one of the most well-known traditionally used herbal medicines caused severe, sometimes fatal cases of interstitial pneumonia.

Challenges associated with pharmacovigilance of herbal medicines:

characteristics Herbal medicine:

Herbal medicinal products (also known as phytomedicines or phytotherapeutic preparations) are "medicinal products containing exclusively herbal drugs or herbal preparations as active substances," i.e.they contain only crude and/or processed plants and/or plant parts as active ingredients; an isolated chemical constituent derived from plant material is not a herbal medicine. Herbal medicines are also used to describe both relatively crude preparations such as herbal tinctures, which are typically supplied by herbal medicine practitioners (medical herbalists), and manufactured or finished herbal medicinal products, which are typically formulated as tablets or capsules and are available for purchase without a prescription.

The constituent profile of a plant is not uniform, and for many plants, only a specific plant part or parts, such as roots or leaves, are (or should be) used medicinally.

Furthermore, the precise constituent profile is likely to differ both qualitatively and quantitatively between batches of herbal starting materials due to one or more of the following factors:

- variation in constituents between and within species
- environmental factors such as climate and growing conditions
- time of harvesting - the profile of constituents can vary even over the course of a day
- post-harvesting factors, such as storage conditions and drying.

Utilisation of Herbal Medicines and Related Issues:

Although there are few reliable estimates of the prevalence of use, the use of herbal medicines is a popular health care approach among patients and consumers in the UK.A cross-sectional survey (n = 5010; response rate: 59%) conducted in 1998 found that 19.8% (95% CI 18.3-21.3) had purchased an over-the-counter herbal medicinal product and 0.9% (95% CI 0.6-1.3) had consulted a medical herbalist in the previous year.

There are currently no longitudinal data for the prevalence of use of herbal medicines in the UK, but market research data show that sales of licenced and unlicensed herbal medicinal products were worth £75 million in 2002, a 57% increase over the previous five years.[7] Studies conducted in other developed countries, such as Australia and the United States, indicate an increase in the use of herbal medicines among the general adult population.[8],[9] Extrapolating estimates of herbal medicine use from such studies indicates that a large number of people are exposed to herbal medicines, which is concerning for public health.

Herbal medicines are used by a diverse range of people in the United Kingdom for both acute and chronic ailments.Many herbal medicinal products are purchased to maintain general health and well-being, as well as to prevent and treat minor, common ailments.Use is not always based on evidence, nor is it limited to symptoms and conditions that can be treated at home.Individuals with serious chronic diseases, such as cancer, AIDS, multiple sclerosis, and asthma, as well as many other conditions, use herbal medicinal products, as do older patients, pregnant or breast-feeding women, and parents/guardians for children.[10] Similarly, medical herbalists use herbal medicines to treat a wide range of ailments.

Some patient groups, such as children and the elderly, are more likely to experience adverse drug effects, and

there is no reason why this should not also be true when they use herbal medicines.Other groups, such as pregnant women, may prefer herbal medicines to conventional medicines because they perceive them to be safer, despite the fact that little is known about the effects of herbal medicines taken during pregnancy.

Typically, users of herbal medicinal products do not seek professional advice when selecting herbal medicines, instead relying on recommendations from friends or relatives and information from popular media.[11],[12] Herbal medicines are widely available for purchase on the internet and in retail outlets where a trained healthcare professional is not present.Even when purchasing herbal medicinal products from pharmacies, a consumer or patient may not interact with a pharmacist or trained pharmacy counter assistant.[13]

Regulation of Herbal Medicines:

The origins of regulation and pharmacovigilance for herbal medicines, as with all medicines, can be traced back to the thalidomide tragedy of the 1950s and 1960s. This was the turning point that resulted in the formation of the Committee on Safety of Drugs (now the Committee on Safety of Medicines, CSM), a 'early-warning system' (the 'yellow card' scheme) for doctors to report their suspicions about adverse drug effects, and legislation in the form of the Medicines Act 1968 requiring pharmaceutical companies to satisfy the competent authority (now the Medicines and Healthcare products Regulatory Agency, MHRA) of the quality of their products.

There are approximately 600 licenced herbal medicinal products on the UK market, though the majority of these are not 'new' marketing authorizations, but rather products that were granted product licences of right (PLRs) when the medicines licencing system was established in 1971.When the competent authority reviewed PLRs for herbal medicinal products, manufacturers of those intended for use in minor self-limiting conditions were allowed to rely on bibliographic evidence to support efficacy and safety, rather than being required to conduct new tests and controlled clinical trials.As a result, while many herbal medicinal products have product licences, they have not necessarily undergone the stringent testing required to obtain a full marketing authorization today, instead relying on evidence from long-standing use.[14]

Adverse Drug Reactions: Herbal remedies may cause adverse drug reactions.Ginkgo biloba causes spontaneous bleeding, St. John's Wort (Hypericum perforatum) causes gastrointestinal disturbances, allergic reactions, fatigue, dizziness, photosensitivity, confusion, and other side effects.Hypertension, cardiac arrhythmias, and myocardial infarction are all caused by Capsicum annuum.Anxiety is caused by ephedra, headaches and diarrhoea by Vitex agnus (Chast tree fruit), and liver toxicity by Piper methysticum.[15]

Drug interactions:Patients who are taking drugs with a narrow therapeutic index, such as Cyclosporine, Digoxin, Phenytoin, Procainamide, Theophylline, Warfarin, and others, should be advised against using herbal products**.**When combined with herbal products, all drugs with a narrow therapeutic index may have increased adverse effects or be less effective.[16] Ginkgo is used to treat Alzheimer's disease and increases bleeding when combined with aspirin.Ginseng has many applications and has a synergistic effect with monoamine oxidase inhibitors.Kava is used as an anxiolytic and has a synergistic effect with benzodiazepines.St. John's Wort is an antidepressant that lowers plasma levels of warfarin, cyclosporine, oral contraceptives, theophylline, and other drugs.Heavy metals are permitted in traditional medicines, but only in specific concentrations specified by ancient physicians.

Heavy metals are permitted in traditional medicines, but only in specific concentrations specified by ancient physicians.There are numerous examples of heavy metal toxicity caused by the use of heavy metals in traditional drug preparations.Lead, copper, mercury, arsenic, silver, and gold, which are frequently added to these preparations, have been linked to toxicity on numerous occasions.Patients should avoid combining herbal medicines with modern medications because there is a risk of drug interactions and adverse drug reactions.[17]

Stability testing: Stability testing of herbal medicines is a difficult risk because the entire herb or herbal product is regarded as the active substance, regardless of whether constituents with defined therapeutic activity are known .[18] The goal of stability testing is to provide evidence on how the quality of herbal products changes over time as a result of environmental factors such as temperature, light, oxygen, moisture, other ingredient or excipient in the dosage form, drug particle size, microbial contamination, trace metal contamination, leaching from the container, and to establish a recommended storage condition and shelf-life.Stability testing is required to ensure that the product continues to be of acceptable quality throughout its storage period.

Stability studies should be conducted on at least three production batches of the herbal products for the proposed shelf-life, which is commonly referred to as long term stability and is carried out under natural atmospheric conditions.

Short term stability data can also be generated under accelerated atmospheric conditions of temperature, humidity, and light, and this data is used to predict the shelf-life of the product.The dosage form packaged in the container closure system proposed for marketing should be subjected to stability testing.It is possible to generate sound stability data for herbal products and forecast their shelf-life using modern analytical techniques such as spectrophotometery and HPLC, as well as by following proper guidelines, which will aid in improving global acceptability of herbal products.[19]

Pharmacovigilance of herbals medicines: Herbal medicines are widely used in both developed and developing countries' health-care systems. However, there have been several high-profile herbal safety concerns in recent years, which have had an impact on public health, and there is a growing emphasis on the need to develop pharmacovigilance systems for herbal medicines. Herbal medicine pharmacovigilance is still in its infancy, and monitoring the safety of herbal medicines presents unique challenges. Although the associated safety risks for some herbal medicines are thought to be low, collective knowledge on the relative safety of herbal medicines remains limited. When applied to herbal medicines, standard pharmacovigilance tools have additional limitations.Adverse effects may be attributed to a pharmaceutical drug even when it is taken concurrently with a herbal product.Inadequate pharmacovigilance procedures invariably result in a relative underreporting of adverse effects.[20]

Need of pharmacovigilance in herbals: To ensure consistency in the naming of herbs in adverse reaction (AR) reports, the WHO collaborating centre for international drug monitoring has recommended the use of proper scientific binomial names for herbs used in medicine, including the use of such names (where this information is available) in the coding of AR reports.This would ensure that reports from various international pharmacovigilance databases are comparable. Authors of published AR case reports must also identify the specific products involved, including label and manufacturer information, specific ingredients, and dose used. Where possible, published case reports would benefit from analysis of the suspect product used for contamination and adulteration, as well as species identification.

Functions of pharmacovigilance: Postmarketing surveillance refers to the monitoring of adverse effects of drugs and herbal remedies as they are used in the general population. Pharmacovigilanceis defined byGood Vigilance Practice (GVP) as drug side effect surveillance in post-marketing safety surveillance. As a result, pharmacovigilance is an important post-marketing tool for ensuring the safety of pharmaceutical and related health products.

According to WHO Guidelines (2000), the four functions of pharmacovigilance are as follows:

• Proactive monitoring and reporting on the quality, 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

• Creating programmes and procedures for collecting and analysing patient and clinician reports.[21]

Methods in Pharmacovigilance

I. Passive Surveillance:

Spontaneous Reporting :

The core data-generation system of international pharmacovigilance is spontaneous reporting, which relies on healthcare professionals to identify and report any suspected ADR to their national pharmacovigilance centre or to the manufacturer.Almost always, spontaneous reports are submitted voluntarily.After a drug is marketed, spontaneous reports play a critical role in identifying safety signals.Alerts to rare adverse events that were not detected in previous clinical trials or other pre-marketing studies.It also contains vital information on at-risk groups, risk factors, and clinical characteristics of known serious ADRs.[22]

One of the system's major flaws is under-reporting, though figures vary greatly between countries and between minor and serious ADRs.Another issue is that overworked medical personnel do not always prioritise reporting; even if the symptoms are serious, they may not be recognised as a side effect of a specific drug.Nonetheless, spontaneous reports are an important component of the global pharmacovigilance enterprise, serving as the foundation of the WHO Database, which contains approximately 3.7 million reports and is growing by approximately 250,000 per year.[23]

Case series: A case report is a notification from a practitioner about a patient who has a disorder that may be caused by drugs.When multiple doctors independently report the same unknown and unexpected adverse effects from a drug, this can be a warning sign.Anaphylaxis, aplastic anaemia, toxic epidermal necrolysis, and Stevens-Johnson syndrome are

some of the more common adverse events associated with drug therapy.

Other reporting methods: Some countries require physicians to report spontaneously.Most countries require manufacturers to submit reports received from healthcare providers to the national authority.Others have intensive, focused programmes focusing on new drugs, even controversial drugs, as well as groups of doctors' prescribing habits involving pharmacists in reporting to generate potentially useful information.

II. **Stimulated reporting:** Stimulated reporting is used to encourage and facilitate the reporting of adverse events by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods using a pre-designed method. Online reporting of adverse events is also one of these methods. Stimulated adverse event reporting in the early post-marketing phase can lead to companies notifying healthcare professionals of new therapies and providing safety information to the general population before they are used by the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan).

III. **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 monitoring of patients taking a specific drug as part of a risk management programme. Patients are asked to complete a brief survey form and consent to future contact. [24]

Sentinel sites: Active surveillance can be done by 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.The chosen sites can provide information data from specific patient subgroups that a passive spontaneous reporting system would not be able to provide.Sentinel sites have several major flaws, including selection bias, a small number of patients, and increased costs.Active surveillance with sentinel sites is most effective for drugs that are primarily used in institutional settings such as hospitals, nursing homes, dialysis centres, and so on.Institutional settings can have a higher frequency of use for certain drug products and can provide a dedicated reporting infrastructure.Furthermore, in certain clinical settings, automatic detection of abnormal laboratory values from computerised laboratory reports can provide an effective active surveillance system.Intensive monitoring of sentinel sites can also aid in the identification of risks in patients taking orphan drugs.

Drug event monitoring: Patients are mostly identified in drug event monitoring through electronic prescription data or automated health insurance claims.A follow-up questionnaire is sent to each prescribing physician or patient at predetermined intervals to collect outcome data.The questionnaire can include information on the patient's demographics, indication for treatment, duration of therapy, dosage, clinical events, and reasons for discontinuation.This method allows for the collection of more detailed information on adverse events from a large number of physicians and/or patients.Poor physician and patient response rates, as well as the unfocused nature of data collection, can all be disadvantages of drug event monitoring.

Registries:A registry is a list of patients who have the same symptom (s).This feature can be a disease (disease registry) or a particular exposure (drug registry).These registries can be used to collect a battery of information in a prospective manner by using standardised questionnaires.Disease registries, such as those for blood dyscrasias, severe cutaneous reactions, or congenital malformations, can aid in the collection of information about drug exposure and other factors associated with a clinical condition.A disease registry can also be used as the foundation for a case-control study comparing drug exposure casesidentified in the registry to controls chosen from patients with another condition in the registry or patients outside the registry.Exposure registries target specific populations who have been exposed to drugs of interest.

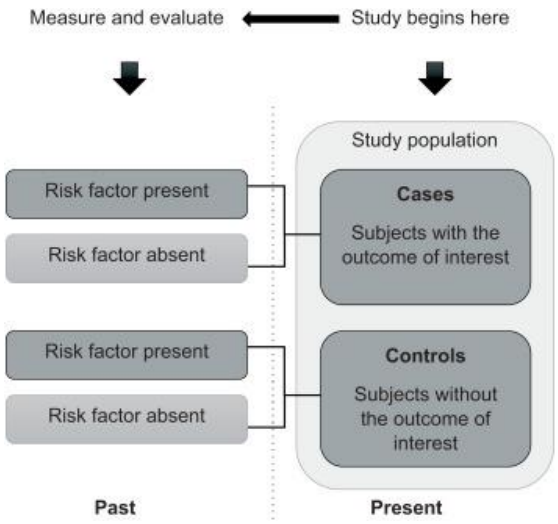
Patients can be tracked over time and enrolled in a cohort study to collect data on adverse events via standardised questionnaires.Single cohort studies can help with signal amplification, especially for rare outcomes.When investigating the safety of an orphan drug indicated for a specific condition, this type of registry can be extremely useful.

IV. **Comparative Observational Studies:** Traditional epidemiologic methods are an important part of evaluating adverse events. A variety of observational study designs can be used to validate signals from spontaneous reports or case series. Cross-sectional studies, case-control studies, and cohort studies are the most common types of these designs (both retrospective and prospective).

Cross-sectional study (survey)

A cross-sectional study is data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status.The term "surveys" refers to the processes by which data is collected and analysed.When data for serial time points are captured and exposures do not change over time, these studies are best used to examine the prevalence of a disease at one time point or to examine trends over time.These studies can also be used to investigate the basic relationship between exposure and outcome in ecological analyses.The main disadvantage of cross-sectional studies is the lack of a direct relationship between exposure and outcome.

Case control study:



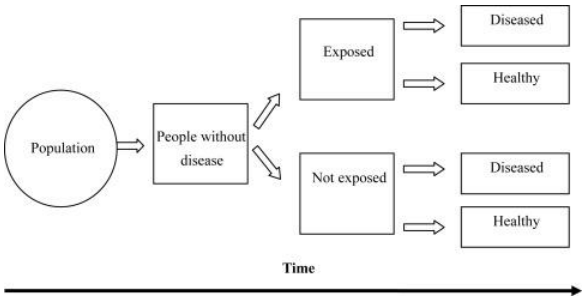
Case-control studies are especially useful when determining whether there is a link between a drug and a single rare adverse event, as well as identifying risk factors for adverse events.

- Cases of disease (or event) are identified.
- Controls, or patient without the disease or event of interest, are then selected from the source population.
- The controls should be sleceted: the prevalence of exposure among the controls

Represents the prevalence of exposure in the source population.

- Exposure status of the two groups is then compared using the odds ratio.

Cohort studies:



Cohort studies are useful when determining the incidence rates of adverse events as well as the relative risks of adverse events.

- A population at risk for the disease (or event) is followed over time for the occurrence of the disease.
- Information on exposure status is known throughout the follow-up and hence incidence rates can be calculated.
- Comparison cohorts of interest are selected on the basis of drug use and followed over time.
- Multiple adverse events can also be investigated using the same data source in a cohort study.[25]

V. Targeted Clinical Investigations:

Specific studies can be conducted to investigate potential drug-drug interactions and food-drug interactions based on the pharmacological properties and expected use of the drug in general practise.Population pharmacokinetic studies and drug concentration monitoring in patients and healthy volunteers are examples of these studies.Potential risks or unexpected benefits in special populations may be identified in pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of patient subpopulations from these clinical studies.Children, the elderly, and patients with co-morbid conditions may metabolise drugs differently than typical clinical trial participants.Additional clinical trials may be conducted in such populations to determine and quantify the magnitude of the risk (or benefit).

A large simplified trial may be conducted 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.To avoid selection bias, patients in a large simplified trial are usually randomised.One limitation of this method is that the outcome measuremay be overly simplified, which may have an impact on the trial's quality and ultimate usefulness.

VI. Descriptive studies:

Descriptive studies are an important component of pharmacovigilance, but they are not used to detect or confirm 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 disease characteristics and disease distribution in specific populations, as well as estimating the incidence and prevalence of potential outcomes of interest.These desirable outcomes now include a description of disease treatment patterns as well as 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

Drug utilisation study :

DUS describe how a drug is marketed, prescribed, and used in a population, as well as how these factors influence clinical, social, and economic outcomes.These studies collect information on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, and are frequently stratified by age, gender, concurrent medication, and other factors.Denominator data derived from these studies can be used to calculate ADR rates.DUS can be used to investigate the difference between recommended and actual clinical practise.These studies can help determine whether a drug has the potential for abuse by looking at whether patients are on escalating dose regimens or if there is evidence of inappropriate repeat prescribing.These studies have significant limitations, such as a lack of clinical outcome data or information on the indication for use of a product.[26]

Implementation status of herbal pharmacovigilance :

Pharmacovigilance entails assessing the risks and benefits of medications and is critical in pharmacotherapeutic decision making.Patients have been increasingly using herbal medicines for several years because the majority of them are available as over-the-counter medication.Herbal medicinal products, like synthetic drugs, require drug surveillance to identify potential long-term risks.

Participants at the WHO Regional Office for South-East Asia's regional workshop on the Regulation of Herbal Medicines recently developed guidelines for the safe use of herbal drugs.[27]

II. CONCLUSION

The use of medicinal herbs as potential therapeutic aids has grown significantly in the global health care system for people, not only in cases of disease but also as potential resources for maintaining good health.[28] It is obvious that the herbal industry has a lot of potential.Given the growing popularity of herbal products, quality issues should be adequately covered in future global labelling practises. Tofully comprehend the use of herbal medicines, standardisation of methods and quality control data on safety and efficacy are necessary.The lack of knowledge about the social and economic advantages that could be obtained from the industrial utilisation of medicinal plants has been a significant barrier to the development of the industries based on medicinal plants in developing countries.To take advantage of the compounds responsible for the biological activity observed, more study is needed.[29]

REFERENCES

[1] Wal Pa, Wal A, Gupta S, Sharma G, Rai AK Pharmacovigilance of herbal Products in India.
[2] WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance system world health organization:Geneva;2004.p.19.
[3] Williamson E. drug interaction between herbal and prescription medicines drug saf1075-92; 26: 2003.
[4] Joanne barnes, pharmacovigilance of herbal medicines a uk perspective,829-851:26(12);2003
[5] European Agency for the Evaluation of Medicinal Products (EMEA) Committee for Proprietary Medicinal Products (CPMP). Note for guidance on quality of herbal medicinal products. CPMP/QWP/2819/00(EMEA/CVMP/814/00) London: EMEA, July 26, 2001 [online].AvailablefromURL:http://www.emea.eu.int/pdfs/ human/qwp/281900en.pdf [Ac- cessed 2003 Aug 13]
[6] Barnes J, Anderson LA, Phillipson JD. Herbal medicines: a guide for healthcare professionals. London: Pharmaceutical Press, 2002
[7] Mintel International Group Ltd. Complementary medicines, UK. April 2003. London: Mintel International Group Limited, 2003
[8] Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a national follow-up survey. JAMA 1998; 280 (18): 1569-75

[9] MacLennan AH, Wilson DH, Taylor AW. The escalating cost and prevalence of alternative medicine. Prev Med 2002; 35: 166-73

[10] Barnes J. Herbal therapeutics (1): an introduction to herbal medicinal products. Pharm J 2002; 268: 804-6

[11] Barnes J, Mills SY, Abbot NC, et al. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. Br J Clin Pharmacol 1998; 45: 496-500

[12] Gulian C, Barnes J, Francis S-A. Types and preferred sources of information concerning herbal medicinal products: face-to face interviews with users of herbal medicinal products [abstract]. Int J Pharm Prac 2002; 10 Suppl.: R33

[13] Quinn CG, Waterman P. A comparison of the teaching of herbal Medicinal Products medicine in the United Kingdom and Europe. University of Strathclyde, 1997

[14] Barnes J, Anderson LA, Phillipson JD. Herbal medicines: aguide for healthcare professionals. London: Pharmaceutical Press, 2002

[15] Kuhn MA, Herbal remedies: drug-herb interactions, Critical Care Nurse, 22, 2002, 22-32.

[16] Hussin AH, Adverse effects of herbs and drug herbal interactions,Malaysian Journal of Pharmacy, 1, 2001, 39-44.

[17] Chauhan VS, Standardizing herbs and intermediates-newer approaches,The Pharma Review, 2, 2006, 37-44.

[18] Kathrin K, Eike R, Anne B, Validation of standardized high performance thin layer chromatographic methods for quality and stability testing of medicines, Journal of AOAC International, 86(5), 2003,909-915.

[19] Manoj S, Raman S, Gupta VB, Chatterjee A, Pharmacovigilance of herbal medicines, The Pharma Review, 12, 2006, 119-124.

[20] Firenzouli, F., et al., Symposium on pharmacovigilance of herbal medicine. London, March 28, 2006

[21] Pharmacovigilance of herbal medicines current status and future strategies 2009

[22] Wiholm, B., et al., Spontaneous reporting systems outside the US. Pharmacoepidemiology. 3rd ed., Wiley Interscience, UK, 2000, pp. 175–192.

[23] Hartmann, K., Doser, A.K., Kuhn, M., Postmarketing safety information: How useful are spontaneous reports. Pharmacoepidemiology and Drug Safety, 1999, 8:S65-S71.

[24] Anonymous., Task Force on Risk Management. Report to the FDA Commissioner. Managing the risks from medical product use: Creating a risk management framework. Part 3, How does FDA conduct postmarketing surveillance and risk assessment, May 1999.

[25] Mackay, F.J., Post-marketing studies. The work of the Drug Safety Research Unit. Drug Safety, 1998, 19:343-53.

[26] Garcia Rodriguez, L.A., Perez Gutthann, S., Use of the UK General Practice Research Database for pharmacoepidemiology. British Journal of Clinical Pharmacology, 1998, 45(5):419-25.

[27] Schulz, V., Hansel, R., Tyler, V.E., Rational phytotherapy: A Physician Guide to Herbal Medicine. 4th ed., Springer, Berlin, 2000.

[28] Verma S, Singh SP, Current and future status of herbal medicines, Veterinary World, 1(11), 2008, 347-350.

[29] Bhanu PS, Sagar TK, Zafer R, Failure and successes of herbal medicines, The Indian Pharmacist, 54(2), 2000,221-235.