International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-1, 2014 ISSN No: 2277 - 7873

REVIEW ARTICLE

Pharmacovigilance of Herbal Drugs: A New Perspective

Dubey SK[1], Anand A*[1], Gupta A[2]

[1]*Department of Pharmacy, Birla Institute of Technology & Science, Pilani, India.*

[2]*Maharaja Surajmal Institute of Pharmacy, New Delhi, India.*

Manuscript No: IJPRS/V3/I1/00034, Received On: 22/01/2014, Accepted On: 30/01/2014

ABSTRACT

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.

KEYWORDS

Adverse Drug Reaction, Herbs, Surveillance, Regulation, Quality Assurance, Adulteration

INTRODUCTION

Herbal medicines sometimes referred to as botanical medicines or herbalism, involves use of plants or parts of plant, to treat injuries or illnesses.[1] Herbal medicines are the study or use of medicinal herbs to prevent and treat diseases and ailments or to promote health and healing.[2] These are the oldest form of healthcare known to mankind.[3] It is major component in traditional medicines and common element in ayurveda, homeopathic, unani and other medicine system.[4]

***Address for Correspondence:**
Amit Anand
Department of Pharmacy,
Birla Institute of Technology & Science,
Pilani-333031, India.
E-Mail Id: amitanand.pharmacist@gmail.com

Thus the use of herbal medicines continues to grow across the world. People are opting herbal medicines or herbal products for their health care. According to a report of WHO United States of America, some US$ 17 billion was spent by more than 158 million Americans in 2000. Recent study indicated that more than 70% of the German population reported using "natural medicines" and for most of them, herbal medicinal products were the first choice in the treatment of minor diseases or disorders. This increased demand has brought with it many challenges about safe use of herbal medicines, bringing into focus the need for formal pharmacovigilance in this field.

Necessity of Pharmacovigilance Studies

An adverse reaction (AR) 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.[5] It is undeniable that plants have an important role in the development of modern medicines. More than 60 to 70% of modern medicines in the world market are directly or indirectly derived from plant products. High-profile issues such as ARs associated with Ephedra and Aristolochia have shown that herbal medicinal products (HMPs) can produce toxicity in human beings. The most common adverse effects reported are hepatic and renal problems. However, it is difficult to identify the causative agent associated with the ARs encountered because traditional herbal preparations often contain multiple ingredients. The WHO database has over sixteen thousand suspected herbal case reports. Due to the lack of clinical trials for most HMPs, postmarket pharmacovigilance is a critical source of safety information; however, the assessment of ARs associated with HMPs offers unique challenges in the quantity and quality of available information.[6,7]

Major causes of such events are adulteration of herbal products with undeclared other medicines and potent pharmaceutical substances, such as corticosteroids and non-steroidal anti-inflammatory agents. Adverse events may also arise from the mistaken use of the wrong species of medicinal plants, incorrect dosing, and errors in the use of herbal medicines both by health-care 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.

Adverse Drug Effects

Herbals are generally considered as harmless since they belong to natural source[8], but these are not entirely free of adverse drug reaction. Some ADR_s of commonly used herbs are spontaneously bleeding by Ginkgo biloba, gastrointestinal disturbances, allergic reaction, fatigue, dizziness by St. John Worth; hypertension, cardiac arrhythmia , myocardial infarction by ephedrine; headache by Paprika, diarrohea by Chast tree fruit and liver toxicity by Piper methysticum.[9]

Drug Interactions

Drugs having narrow threrapeutic index such as digoxin, theophylline, phenytoin etc. should not be used with herbal medicines.[10] They may either have increased ADR_S or be less effective when used in conjunction with herbal products. Ginkgo biloba is used for Alzheimer's disease and causes increased bleeding with aspirin. Ginseng has multiple uses and causes synergism with monoamine oxidase inhibitors. Kava is used as anxiolytic and shows synergism with benzodiazepines. St. John's Worth is used as antidepressant and cause reduced level of warfarin, cyclosporine, oral contraceptives, and theophylline.[11] Heavy metals such as lead, copper, mercury arsenic, silver and gold are used in traditional medicines have caused toxicity on many occasions.

Pharmacovigilance of Herbal Drugs

Pharmacovigilance is a French term referring Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[12,18] It involves monitoring of safety of drug over the period of time, identification of ADR_S in humans and access risk –benefit ratio.[13] Pharmacovigilance protect the patients from unnecessary harm by identifying previously unrecognized drug hazards, elucidating pre-disposing factors and quantifying risk in relation to benefits.[14] The pharmacovigilance of herbal medicines exhibits particular challenges because such preparations are available from wide range of outlets typically where there is no health care professional available, most purchases are in conventional OTC environment. Various methods in pharmacovigilance are passive surveillance which includes spontaneous reporting and stimulated reporting, active

surveillance by sentinel sites, drug event monitoring, registries, comparative observational studies by survey study, case control study, targeted clinical investigations by investigate drug –drug interaction and food drug interactions.[15] The importance of genetic factors in determining the individual susceptibility to adverse reaction is well documented and this implies to herbal medicines as well as to conventional drugs. Pharmacovigilance is therefore, one of the important post-marketing safety tools in ensuring the safety of pharmaceuticals and related health products.[16]

Despite the growing interest in the safety of herbal medicines, national surveillance systems to monitor and evaluate adverse reactions associated with herbal medicines are rare, even among the more than 70 Member States participating in the WHO International Drug Monitoring Programme. A recent WHO survey showed that around 90 countries, less than half of WHO's Member States, currently regulate herbal medicines and an even smaller proportion has systems in place for the regulation/qualification of providers of herbal medicines. National pharmacovigilance systems should be closely linked to national drug regulatory systems. To function properly, a national safety monitoring programme for herbal medicines should be operated alongside an effective national drug regulatory system 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.[17,18]

Challenges in Monitoring Safety of Herbal Medicines

Regulation

National regulation and registration of herbal medicines vary from country to country. According to regulatory frame work of country herbal products may be categorized as either prescription or OTC medicines. The national regulatory framework usually also includes involved qualified providers and distributors of the respective substances. Regulatory status consequently determines the access to or distribution route of these products.[19]

Quality Assurance and Control

Quality assurance and control measures, such as national quality specification and standards for herbal materials, good manufacturing practices (GMP) for herbal medicines, labeling, licensing schemes for manufacturing, imports should be in place in every country where herbal medicines are regulated.[20] These measures are vital for ensuring the safety and efficacy of herbal medicines. Weak regulation and quality control may result in a high incidence of adverse reactions attributable to poor quality of herbal medicines, in particular, resulting from adulteration with undeclared potent substances and/or contamination with potentially hazardous substances and residues.

The requirements and methods for quality control of finished herbal products, particularly for mixture herbal products, are far more complex than for other pharmaceuticals. The quality of such products is influenced by the quality of the raw material used. Good agricultural and good collection practices for medicinal plants, including plant selection and cultivation are therefore, important measures.

Safety Monitoring of Herbal Medicines

The most common sources of information on adverse events and reactions to medicines are clinical trials and spontaneous reports (voluntary, unsolicited communications on marketed medicinal products). The latter ordinarily far exceed the former in numbers and type, especially serious reports over the lifetime of a product. In some countries adverse reaction reporting by physicians is mandatory; such reports are regarded as spontaneous.

In many countries, providers of herbal medicines other than physicians, dentists, pharmacists, and nurses are excluded from reporting systems. If adequate coverage of herbal medicines is to be achieved, national reporting schemes should be developed to include all providers of herbal medicines (both prescribers and dispensers) and providers of

traditional and alternative medicine according to national circumstances.

A substantial proportion of herbal medicines are over the counter drugs OTC medicines, and many come directly into this category without prior postmarketing safety monitoring as prescription medicines. It is therefore, most important to take measures to strengthen pharmacovigilance activity in the OTC medicines setting. Community pharmacists and nurses can play a particularly useful role in monitoring the safety of OTC medicines, although many such products are sold outside pharmacies. The involvement of consumers in the use of herbal medicines, herbal products in health care and their concern regarding possible adverse effects should be valued positively. Consumer reports on adverse reactions should be accepted as an important source of information, which can contribute to the identification of signals for unknown effects of herbal medicines.

Recording and Coding the Identity of Herbal Medicines

Use of a standardized classification and identification for transmitting reports to the UMC is desirable. Coding of adverse events/adverse reactions to herbal medicines should be compatible with that for other medicines. The UMC, therefore, proposes the use of the WHO Drug Dictionary (WHO-DD), as it has been developed to store structured, classified information on the names of herbal products and their ingredients in the same way as similar information on other medicines.

For the therapeutic classification of herbal products, the UMC proposes the herbal anatomic–therapeutic–chemical (HATC) classification, which is structurally equivalent to the anatomic–therapeutic–chemical (ATC) classification used for chemical substances in other medicines. HATC is being implemented within the WHO-DD structure as part of the global WHO database. A combination of the use of the HATC classification and the expanded global WHO database structure can manage all levels of data input, however imprecise. In addition, the UMC also proposes a system checklist for cross-referencing of botanical and vernacular names used as names of ingredients. The UMC suggests that the WHO-DD, the HATC classification and the checklist should prove useful tools for the national pharmacovigilance centers when asking questions of the reporter to increase the clarity and accuracy of reports.

Herbal medicines usually contain multiple ingredients and it is not always possible to identify them all. In such cases, the product name should be recorded and referred to the UMC, which will assist with identification. If the product is not already in the global WHO database, it will be added together with the available information. A particular herbal product may have a number of indications and therefore appear in several places in the HATC classification.[21]

Local input by the reporter as to the precision or otherwise of the information on the product is most useful. This can be provided in free text, as a commentary on the report, or by the submission of the manufacturer's information or the original packaging. A national inventory or catalog of medicinal plants may also serve as a reference on medicinal plants and their use in the community. In many countries, however, knowledge of medicinal plants and their medicinal use has not been documented. The establishment of a national inventory or catalog should, therefore, be encouraged.

If the finished herbal product concerned or its raw materials were imported from other countries, the drug regulatory authority of the exporting country may be able to provide helpful information.

The precise Latin binomial botanical name (genus, species, author; as well as name of family) of the medicinal plants concerned should be used whenever possible, together with information about the plant parts used and the extraction and preparation methods employed. This information allows accurate comparison with other reports. A common vernacular name may be used in order not to delay or cancel the

submission of a report. National pharmacovigilance centers should collaborate with the pharmacognosy departments of universities and with botanists, zoologists, and botanical garden staff regarding taxonomic (botanical and chemical) identification and botanical and vernacular nomenclature.

Data Management[22]

Data Quality

Strenuous efforts should be made to ensure that there are quality controls on data processing and the data elements of reports are as complete and accurate as possible. Mechanisms to check for duplications should be instituted.

Data Storage

Computer databases should be managed to as high a standard as possible to facilitate access to and use of the data. Software should be selected with expert advice so that analytic needs can be met.

Data Analysis

Programs should be developed to provide for regular analyses and data output appropriate for local needs.

Regulatory Status of Herbal Medicines

The legal status of herbal medicines differs from country to country. Developing countries have folk knowledge of herbs and their use in traditional medicines is widespread. But, these countries do not have any legislative criteria to include these traditionally used herbal medicines in drug legislation.[23]

Approval of herbal medicines in most countries is based on traditional herbal references, provided they are not known to be unsafe in treating minor illnesses. But, now day's claims are being made to treat serious illnesses with herbal medicines for which no traditional knowledge is present.[24] Therefore, regulatory requirements for herbal medicines are necessary to ensure safety, efficacy and quality to support specific indications, scientific and clinical evidences must be acquired.[25]

CONCLUSION

Medicinal herbs have attained significant role in health care system not only as therapeutic aid but also in maintaining proper health. It is well known that herbal medicine industries have made great progress but, they should be encouraged adequately address quality aspects. Standardization of methods and quality control data on safety and efficacy are required for understanding the use of herbal medicines. Therefore, herbal medicine monitoring should be included in the national pharmacovigilance program. Doctors, nurses and pharmacist should be motivated to report ADR_S and should be made aware of process of reporting .The success of monitoring will depend upon awareness about National Pharmacovigilance Program among health care professionals.

REFERENCES

1. Winslow, L. C., & Kroll, D. J. (1998). Herbs as medicines. *Archives of Internal Medicine*, *158*(20), 2192-2199.
2. Gossell-Williams, M., Simon, O. R., & West, M. E. (2006). The past and present use of plants for medicines. *West Indian Medical Journal*, *55*(4), 217-218.
3. De Smet, P. A. (1997). The role of plant-derived drugs and herbal medicines in healthcare. *Drugs*, *54*(6), 801-840.
4. Abhishek, K., Ashutosh, M., & Sinha, B. N. (2006). Herbal drugs-present status and efforts to promote and regulate cultivation. *The Pharma Review*, *6*, 73-77.
5. Health Canada, 2009a. Release of the guidance document for industry - reporting adverse reactions to marketed health products. 2009. Jul 09,(last accessd on 19.4.13):http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2009-guidance-directrice_reporting-notification/index-eng.php
6. Farah, M. H., Edwards, R., Lindquist, M., Leon, C., & Shaw, D. (2000). International monitoring of adverse health effects associated with herbal

medicines. *Pharmacoepidemiology and Drug Safety*, *9*(2), 105-112.

7. Gardiner, P., Sarma, D. N., Dog, T. L., Barrett, M. L., Chavez, M. L., Ko, R., & Giancaspro, G. I. (2008). The state of dietary supplement adverse event reporting in the United States. *pharmacoepidemiology and drug safety*, *17*(10), 962-970.
8. Harish, P. (2001). Herbal drugs, *Current science. 81(1)*. 15.
9. Vikas, D. Sindhu, S. Swati, P. Chawla, A. (2003). Adverse drug reaction of herbal drugs. *Indian Academy of Clinical Medicines. 4(4).* 345-347.
10. Kuhn, M. A. (2002). Herbal remedies: drug-herb interactions. *Critical care nurse*, *22*(2), 22-32.
11. Hussin, A. H. (2001). Adverse effects of herbs and drug-herbal interactions. *Malaysian Journal of Pharmacy*, *1*(2), 39-44.
12. Manoj, S. Raman, S. Gupta, V. B. Cateerjee, A. (2006). Pharmacovigilance of herbal medicines. *The Pharma Review*. *12*. 119-124.
13. Chan, T. Y. (1997). Monitoring the safety of herbal medicines. *Drug safety*, *17*(4), 209-215.
14. Kshirsagar, N. (2005). The pharmacovigilance system in India. *Drug safety*, *28*(7), 647-650.
15. Bigoniya, P. (2009). Pharmacovigilance of herbal medicines: current status and future strategies. *The Pharma Review*, *5*, 77-88.
16. Chan, T. Y. (1997). Monitoring the safety of herbal medicines. *Drug safety*, *17*(4), 209-215.
17. World Health Organization. (2004). WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems.
18. World Health Organization. (2002). Safety of Medicines: a guide to detecting and reporting adverse drug reactions. *Geneva: World Health Organization*.
19. Report of CIOMS Working Group V. Geneva: The Council for International Organizations of Medical Sciences. (2001). *Current challenges in pharmacovigilance*: Pragmatic approaches.
20. The use of essential drugs. Sixth report of the WHO Expert Committee. Geneva: World Health Organization. (1995). *Who Guidelines for Good Clinical Practices (GCP) for Trials on Pharmaceutical Products*. World Health Organization, 1994.
21. Stephens, M. D. B., & Talbot, J. C. C. (1985). *The detection of new adverse drug reactions*. Stockton Press.
22. WHO Drug Dictionary. Uppsala Monitoring Centre electronic database, updated quarterly. Available from: http//www.umc-products.com/ [last accessed on 2013 0ct 30]
23. Sukhdev, S., Arun, N., & Kalia, A. N. (2008). Patentability of herbal products: a review. *The Pharma Review*, *4*, 118-124.
24. Raskin, I., Ribnicky, D. M., Komarnytsky, S., Ilic, N., Poulev, A., Borisjuk, N., & Fridlender, B. (2002). Plants and human health in the twenty-first century. *TRENDS in Biotechnology*, *20*(12), 522-531.
25. Mukherjee, P. K. (2003). Exploring botanicals in Indian system of medicine-Regulatory perspectives. *Clinical research and regulatory affairs*, *20*(3), 249-264.

