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**PHARMACOVIGILANCE AND ITS RELEVANCE TO SIDDHA SYSTEM****MEENA R\*<sup>1</sup> AND RAMASWAMY R S<sup>2</sup>***\*<sup>1</sup> Ph.D scholar, National Institute of Siddha, Tambaram sanatorium, Chennai-47.**<sup>2</sup> Director General, CCRS, Chennai-106.***ABSTRACT**

Existence of Siddha system of medicine can be traced to ancient times. It has survived the onslaught of various other systems of medicines proving its efficacy. Siddhars were experts in medicine preparations which cured innumerable diseases. Pharmacovigilance is defined as the science of detection, assessment, understanding and prevention of adverse drug effects or any other possible drug related problems. Although the term pharmacovigilance is actually not featured in Siddha texts, it is vibrant throughout literature. This paper deals with the historical perspectives, adverse drug reactions in Siddha system, need for pharmacovigilance, challenges faced, pharmacovigilance of clinical trials, measures to improve pharmacovigilance of herbal medicines and future suggestions.

**KEY WORDS:** Siddha system, Pharmacovigilance, Adverse drug reactions, Clinical trials, Herbal medicines.

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## INTRODUCTION

The Siddha system of medicine is one of the Indian systems of medicine. This system of medicine is practiced widely in Tamil Nadu, India. The word 'SIDDHA' comes from the word 'SIDDHI', which means an object to be attained or perfection or heavenly bliss. Siddhars, the founders of this system were popular writers in Tamil.<sup>1</sup> The fundamental principles and doctrines of Siddha system shows close similarity to Ayurvedha system, with its specialization in Iatro chemistry. According to Siddha system, our body is nothing but the replica of this Universe. It is also applicable to food and drugs irrespective of their origin.<sup>2, 3</sup> In the recent past, there is a growing global interest in knowing all about this system of medicine. Their awareness prompts them to take to this system of medicine. The need for pharmacovigilance is more than ever before.<sup>4</sup> Pharmacovigilance is the assessment of risks and benefits of medicines. It plays an important role in Pharmacotherapeutic decision making. The present models of pharmacovigilance and its associated tools have been developing in relation to synthetic drugs. Safety monitoring of herbal medicines is improved by modifying existing methodology, patient reporting greater consideration of pharmacogenetics and pharmacogenomics in optimizing the safety of herbal medicines.<sup>5</sup> Pharmacovigilance applies throughout the lifecycle of a medicine both to the pre-approval stage and the post approval. No medicinal product is entirely or absolutely safe for all people in all times. We must always live with some measures of uncertainty. Pharmacovigilance can characterize that risk. Spontaneous reporting is the core data-generating system of International pharmacovigilance, relying on health care professionals (and in some places consumers) to identify and report any suspected adverse drug reactions to their National pharmacovigilance centre or to the manufacturers.<sup>6</sup> The Siddha system cannot remove itself from the application of pharmacovigilance.

### PHAMACOVIGILANCE-HISTORICAL PERSPECTIVE

#### a. What is pharmacovigilance?

Pharmacovigilance is defined as the science of detection, assessment, understanding and prevention of adverse drug effects or any other possible drug related problems.<sup>7, 8</sup> Pharmacovigilance is a French term. It refers to identifying side effects of drugs, their treatment, documentation, reportage and regulatory decisions based on them.<sup>9, 10</sup> Man must have experienced the adverse drug reactions when he first started using plants as medication and evidence of awareness to adverse drug effects can be observed in literature.

#### b. Pharmacovigilance before 18th century:

The use of drugs and pharmacovigilance go hand in hand. Hence the genesis of the science of pharmacovigilance can be traced long before the 18<sup>th</sup> century. In 1780 BC Babylonian code of Hammurabi gives details of punishment for harm done by medical procedures. The punishments were deterrent and severe. According to the said code "If a doctor make a large incision with the operating knife, and kill him or open a tumour with the knife, and cut out the eye the hands shall be cut off." As far back as the 10<sup>th</sup> century the Salerno medical school was empowered to inspect drugs for possible adulterations and severe penalties were imposed: "Whosoever shall have or sell any poison or noxious drug not useful or necessary to his art, let him be hanged." was the dictum. There were provisions for the supervision of sales of drugs and poison by King James VI of Scotland<sup>11</sup>.

#### c. Pharmacovigilance in the 18th century:

During the 18<sup>th</sup> Century, the issues 'side effects' caused by the drugs were addressed properly as it is seen below:

An English physician William Withering (1741-1799) published his extensive work on foxglove in 1785. This work was later recognized as the first systematic paper on a medicinal drug with detailed description of adverse effects associated with digitalis treatment. He laid emphasis on the proper measurement of doses. In 1789, Wouter van Doeveret, Professor of Medicine at Leiden University viewed that many illness may result from inappropriate treatments administered without proper diagnosis. He sounded a

warning that a second ailment may be added to the first or perhaps the death may result as a consequence of empirical treatment. In 1861 Oliver Wendall Holmes went to the extent of saying, "If the whole Materia Medica as it is used now would be sunk to the bottom of the sea, it would be all the better for mankind-and all the worst for the fishes."

**d. Pharmacovigilance in 19th century:**

The early period of the 19<sup>th</sup> century had seen the records of systematic reporting of adverse effects associated with therapeutic measures. Example: Cow pox vaccine, Chloroform anesthesia.

**e. Pharmacovigilance in 20th century**

The 20<sup>th</sup> century saw an increased awareness in the area of pharmacovigilance.

**Pre thalidomide era**

In this era, drug manufacturing came under the supervision of the authorities. The FDA was established in 1906 to impose quality criteria for drug manufacturing and many pharmacopoeias came into existence. 1938 was the landmark year when more stringent safety were initiated and legislated in response to Sulfanilamide disaster.

**Thalidomide disaster and post thalidomide era**

The pharmacovigilance system underwent significant changes worldwide in the wake of the thalidomide disaster of the year 1961. The regulatory authorities, industry and health care workers were involved in the system. Keeping in view the need for the instant detection of the drug related adverse reactions and prevention of the tragedies of the kind of 1961; post marketing surveillance system in the government organization was insisted.

**PHARMACOVIGILANCE-THE CURRENT STATUS**

In 2002, WHO publication "The importance of Pharmacovigilance" laid down the guidelines for implementation of pharmacovigilance program at International level. CIOMS-Council for International Organization of Medical Sciences and ICH International Conference on Harmonization along with national regulatory authorities and pharmaceutical industry focused

their attention on pharmacovigilance and they were instrumental for its world wide development. It was in the year 1986, a formal drug safety monitoring system was proposed for the first time in India. With the help of WHO, three adverse drug reaction monitoring centers were identified.

A. National pharmacovigilance centre at AIIMS, New Delhi and

B. Two WHO special centers at Mumbai and Aligarh.

With the help of modern computer technology empiric Bayesian (data mining) algorithms is systematically applied to large drug safety databases. This is to identify higher- than-expected reporting relationship between drugs and events<sup>12-21</sup>

**NEED FOR PHARMACOVIGILANCE:**

The drugs that are not subject to pharmacovigilance may not be safe. Effective pharmacovigilance system ensures the safe use of drugs. Pharmacovigilance must be given prime of place for more than one reason. They include:

**1. Questionable and unreliable preclinical safety data**

Well – controlled and selected conditions.

Small and specific sample size favoring the result.

Pressure from various groups to shorten the time to approval.

**2. Pharmaceutical marketing strategies according to the prevailing conditions**

Aggressive marketing to meet the competition.

Direct to consumer advertising, taking them for a ride.

Launch in many countries at a time to create an impact.

**3. Influence of medical advancement in physician and patient preferences**

Increasing use of hitherto unknown new drugs.

Increasing use of drugs to improve quality of life without other considerations.

Shift of supervised to self administered therapy exposing to risks.

**4. Easy availability and accessibility**

Going for OTC drugs due to ignorance.<sup>22</sup>

Easy access by internet and lack of medical knowledge to handle the drugs.  
Easy availability of complementary medicines.  
Easy availability of substandard drugs.

### 5. Clinical trial and its Limitations

Homogenous population sample  
Specific inclusion / exclusion criteria.  
Confines the subject to single disease and  
No space for Specific groups of children, elderly and pregnant.  
Small sample size makes it difficult to detect the rare adverse event.  
Short duration of trial has the drawback of limiting the detection of long term adverse effects and not detecting adverse reactions under real conditions namely,  
Drug interaction.  
Drug food interaction.  
Other unpredictable conditions and  
Risk factors.<sup>23</sup>

### ADVERSE DRUG REACTIONS AND SIDDHA SYSTEM

It is not correct to say that Siddha drugs are always without side effects.<sup>24</sup> The use of the drugs may give room for side effects if mistake occur anywhere, ie, herbs cultivation, raw drug selection, purification, prescription, dosage, duration of treatment, age, body condition and diet intake of patients, physical and mental status of the patient.<sup>25</sup> Care should be given to these factors, in order to avoid any adverse reactions or serious adverse reactions during the course of use of the drugs. Few examples are

a. *Aconitum ferox* ( *Nabi* )- excess consumption results in toxic manifestations such as deep syncope, vomiting, tongue, mouth and face become excised due to pungent taste and loose their sensation, abdominal colic, blood stained diarrhoea with tenasmus, hallucination.

b. *Calotropis gigantea* ( *Erukku* )-latex of this plant if consumed in excess amount causes gastritis, stomatitis , vomiting and diarrhea.<sup>26</sup>

### Identification of adverse drug reactions

The adverse drug reaction classifications, which are applicable to the allopathy system is applicable to the herbal medicines as well.<sup>27</sup>

Type a- acute/ augmented-dose related

Type b- bizarre/ idiosyncratic-not dose related

Type c -chronic/ cumulative

Type d- delayed onset-carcinogenic, genotoxic.

### Minimum requisites for detection of adverse drug reactions

Guidelines are in vogue to know the adverse events.<sup>28</sup> The essential case details are patient demographics, relevant medical history, symptoms, abnormal lab reports, drug identification, usage, dose, treatment duration, details of adverse reactions. For compound drugs botanical name, chemical name of ingredients is required.

### Pharmacovigilance of herbal drugs

From time immemorial herbal medicines are known to be in practice.<sup>29, 30, 31</sup>.WHO defines herbal medicines as a broad term that includes herbs, herbal materials, herbal preparations and finished herbal products. (WHO/EDM/TRM/2000.1.)

The traditional use of herbal medicines has long historical basis, on the basis of which they are widely acknowledged to be safe and effective. WHO estimates that about 80% of population in developing countries relies on traditional medicines, at least for primary health care. Conventionally, the traditional systems of medicine enjoy mass appeal and faith and have been labeled as "effective and safe". Systematic literature search reveals that these drugs are being implicated with both therapeutic as well as adverse drug reaction.

Unlike conventional drugs, herbal products are not regulated for purity and potency. Thus, impurities, undeclared adulteration, mineral contamination, batch to batch variation , are some of the constant threats in their usage and can also justify many of the reports on their toxic effects.<sup>32, 33</sup> Surveys say that consumers receive many herbal drugs without prescription from doctor. Patient fails to admit that they take herbal medicine . Thus, Abbot et al and De Smet has stated that 'herbal drugs are safe' is a misnomer and adverse drug reactions with herbal drugs are a reality. The intensity of ADR can not be marginalized, as they can even prove to be fatal .<sup>34</sup> Siddha system does not stop with mentioning of adverse drug reactions alone. Siddhars have told the antidotes for those poisoning. To quote few examples,

- a. Semecarpus anacardium (*Serankottai*)-boiled tender coconut pulp and water.
- b. Plumbago zeylanica root bark (*Chithira moola vaer*) – cow's ghee.<sup>35</sup>

### **SOME CASE REPORTS REGARDING ADR OF HERBAL DRUGS**

Kshirsagar et al in the year 1992 has stated that two patients taking Phenytoin 300mg/day, who had well controlled seizures, presented with sudden loss of seizure controls. A close history taking revealed that they had started taking "Shankapushpi". Single dose administration of the drugs did not lead to any change in Phenytoin levels but decreased its antiepileptic effect.<sup>36</sup> Ginkgo biloba cause spontaneous bleeding, St. jhon's wort (*Hypericum perforatum*) cause spontaneous gastrointestinal disturbances, allergic reactions, fatigue, dizziness, photosensitivity, confusion, adverse reactions with Capsicum annum are hypertension, cardiac arrhythmias, myocardial infarction, Ephedra results in anxiety, Vitex agnus (*Chast tree fruit*) causes headache, diarrhea and Piper methysticum causes liver toxicity.<sup>37</sup> The most commonly reported reactions are pruritis, rash, urticaria, Rash erythematous, nausea, vomiting, diarrhea, headache, abdominal pain, fever. In an International symposium on pharmacovigilance of herbal medicines, held in London on March 28, 2006, a total number of 41439 ADR were listed as due to herbal drugs.

### **CHALLENGES FACED BY HERBAL DRUGS**

Herbal medicines are in use since ancient civilization.<sup>38</sup> Adverse effects or toxicities associated with herbal drugs are challenging. These challenges are not normally encountered with modern system of medicine.<sup>39</sup>

- ❖ Ambiguity over nomenclature.
- ❖ Variability in content due to diverse climatic conditions.
- ❖ Subjective interpretation of traditional descriptions.
- ❖ Batch to batch variation in a challenging issue regarding quality control.
- ❖ These are contributed towards errors in the preparation of the products.
- ❖ Identification of medicinal plants.
- ❖ Adulteration of herbal medicines.

- ❖ Lack of proper knowledge about herbal medicines amongst the providers and consumers.
- ❖ Identification and use of medicinal plants in various preparations.
- ❖ Deliberate and native adulteration of herbal medicines.
- ❖ Liberal use of heavy metals in formulations.
- ❖ Lack of proper knowledge on herbal medicines amongst the providers and consumers.
- ❖ Wide prevalence of self medication amongst users of herbal medicine.
- ❖ Limited pharmacological data on the therapeutic and safety profile.
- ❖ Inadequate and lenient implementation of regulations regarding quality standards for their manufacture, packaging sale and use.
- ❖ Weak national quality assurance measures for labeling, licensing schemes for manufacturing, importing and marketing of herbal products.
- ❖ Disparities in regulation of herbal medicines between countries.
- ❖ Unpredictable herb to herb interactions and herb-food interactions are major contributors of ADR.

### **Prime challenge with Siddha drugs**

Unlike allopathic drugs, the special characteristics of Siddha drugs are compound formulations consisting of many ingredients in single formulation. So, standardization procedure poses a problem. Variety of factors influence chemical profile of a drug. The following are some of them:

- Geographical origin
- Genotype of herbs
- Parts collected
- Time and conditions of harvesting
- Storage methods
- Processing and extraction techniques.<sup>40</sup>

### **WHAT AN ACTIVE PHARMACOVIGILANCE PROGRAM REQUIRES**

- An active pharmacovigilance program requires
- ❖ Strict adherence to the guidelines laid down for reporting adverse events on herbal medicines.
  - ❖ Taking up the incidents for a thorough skilful technical investigation and sharing of data from the angle of pharmacovigilance.

- ❖ Not ruling out adverse events and taking steps to probe the systematic weakness those are potential for adverse events.
- ❖ Identifying and availing the existing knowledge resources, within and outside the health care sector.
- ❖ Making the healthcare delivery system effective, so that structures are reconfigured, incentives are realigned, and safety and quality are placed at the core of the system.

#### **AIM OF THE PHARMACOVIGILANCE PROGRAM**

- ❖ Early detection of hitherto unknown adverse reactions and interactions.
- ❖ Detection of increases in frequency of known adverse reactions.
- ❖ Identification of risk factors and possible mechanism underlying adverse reactions.
- ❖ Undertaking benefits/risk from the quantitative aspects.<sup>41</sup>
- ❖ Improve public health and safety in relation to use of medicines.
- ❖ Taking all possible steps to make people aware of what pharmacovigilance is.<sup>42</sup>

#### **NEED OF A SOUND PHARMACOVIGILANCE PROGRAM:**

The need of a sound pharmacovigilance program can be understood by the various issues it is meant to address, namely;

- ❖ Formulations of drug regulations.
- ❖ Creating data base.
- ❖ Classifying and coding the traditional medicines in internationally accepted format of WHO's herbal ATC (Anatomical-Therapeutic-Chemical) classification.
- ❖ Insufficient evidence of safety from clinical trials.
- ❖ It will be horrible if medicines turn to be fatal. The administration of drugs is to save the lives and that should be the guiding factor. Pharmacovigilance is aimed at it.<sup>43</sup> It has been suggested that ADRs may cause 5700 deaths per year in UK.<sup>44</sup> ADRs were 4<sup>th</sup> – 6<sup>th</sup> commonest cause of death in US in 1994.<sup>45</sup>
- ❖ To keep products on the market.
- ❖ To protect patients from unnecessary harm. (Many adverse events are preventable).
- ❖ To reduce health care expenses ADRs are a huge burden.
- ❖ Because any medicine can be implicated.

- ❖ Promoting rational use of medicines and adherence.
- ❖ Ensuring public confidence.
- ❖ Ethical thing to do. To know of something that is harmful to another person who does not know, and not telling, is unethical.
- ❖ Exposing the inherent adverse events.<sup>46</sup>

#### **MEASURES TO IMPROVE THE PHARMACOVIGILANCE OF HERBAL MEDICINES**

- ❖ Conduct randomized controlled clinical trial (RCT). RCT remain gold standard for establishing the safety and efficacy of any intervention. It can easily identify adverse events. However, some stumbling blocks that remain are – a. use of placebo, b. blinding appropriate standard, c. evaluation of paradigms, etc.
- ❖ Training of practitioners in recognizing and reporting adverse events.
- ❖ Introduction of package inserts for herbal medicines.
- ❖ Public education.
- ❖ Incorporation of safety monitoring of herbal medicines as part of routine safety monitoring.
- ❖ Stringent regulations regarding quality and purity.

#### **CLINICAL TRIALS AND PHARMACOVIGILANCE: INDIAN SCENARIO**

Drugs though have benefited mankind; it has equally produced adverse reactions.<sup>47</sup> Pharmacovigilance is a part and parcel of clinical research.<sup>48, 49</sup> Clinical research is currently in the news for its immense business potential in India. "Efficacy" of a new molecule can be demonstrated through 'positive findings' (results) that indicate its therapeutic usefulness. On the other hand "safety of the new molecule can only be established by its "lack of relative risk" to the patients. This can be done only if the trial subjects on study medication are closely and diligently monitored for "possible" adverse experiences (reactions-during the study). Though preclinical toxicity studies and randomized clinical trials act as indicators of adverse events, such studies are not fool proof to assess possible adverse events that may occur when the drug is used in clinical practice.<sup>50</sup> Recognition of less obvious adverse drug reactions require clinical alertness, accurate diagnosis and

understanding of principles of causality assessment.<sup>51</sup>

### **PHARMACOENVIRONMENTOLOGY**

Pharmacoenvironmentology is a new concept. Syed Ziaur Rahman is behind this. This came to be used only after 2006.<sup>52</sup> It is a form of pharmacovigilance. It deals with those pharmacological agents that have impact on the environment through living organisms subsequent to pharmacotherapy.<sup>53, 54, 55</sup> As Indians are aware, with increasing number of doctors and hospitals of India can boast of a global clinical trial hub. Whenever new drugs are being introduced in India measures are in place to protect the population from their potential harm.<sup>56</sup> As far the medicinal plants used for therapeutic purpose most of them are plant based. The use of these medicines is not limited to the boundary of our country. Other countries are also envious keen interest on them.<sup>57</sup> Use of herbal medicine is wide spread in developing as well as developed countries.<sup>58</sup> The use of plant based health products was also increased in other European countries

### **CONCLUSION**

There is a widening circle of uses of our herbal medicines. No doubt it is a credit to the traditional Siddha system. Our concern is now about the safe use of the drug for which they should also be brought under pharmacovigilance. Onus rests on us to prove that Siddha system yields to pharmacovigilance discussed above. So far, a few well-controlled double-blind (placebo-controlled) trials have been carried out with herbal medicines. Reverse pharmacological studies are carried out for many classical Siddha preparations. Many Siddha hospitals in India have established Pharmacovigilance team to monitor the safety and efficacy of clinical trials. Recent meta-analysis of reviews published in important medical journals, such as the Annals of Internal Medicine, the Journal of the American Medical Association (JAMA), the British Medical Journal, the Lancet, and the British Journal of Clinical Pharmacology, among others, confirms this assumption.

### **REFERENCES**

1. T.V.Sambasivampillai, Tamil-English dictionary of Medicine, Chemistry, Botany and Allied sciences, 13-14, first edition-1931, 2<sup>nd</sup> edition 1991, vol29, Directorate of Indian medicine and homoeopathy, (1994).
2. S S Agarwal, M Paridhars, Herbal drug technology, University press pvt ltd 2007, reprint, 13, (2009).
3. C.S.Uthamarayan, A compendium of Siddha doctrine, Department of Indian medicine and Homoeopathy, First edition-(2005).
4. Conference proceedings- viii International conference, Lublin, Poland, Chemistry for protection of the environment, (September 16-18, 1991).
5. 5, 6, 11, 34, 36. SK Gupta, Textbook of Pharmacovigilance, Jaypee Brothers Medical Publishers (p) ltd, 142-155, (2011).
6. The Importance of Pharmacovigilance, Centre for International Drug Monitoring (2007). Available at <http://www.who-umc.org>. Cited 18 Dec (2007).
7. The Importance of Pharmacovigilance, World Health Organization (2002).
8. Evans SJW, Pharmacovigilance: A science or fielding emergencies. Statistics in medicine, 19: 3199-3209, (2000)
9. Chan TY, Monitoring the safety of Herbal medicines. Drug safety, 17: 209-215,( 1977).
10. Du Mouchel W, Pregibon D, Empirical Bayes screening for multi-item associations. In: Proceedings of the seventh ACM SIGKDD International conference on knowledge discovery and data mining, San Diego, CA,( August 26–29, 2001). New York: ACM Press, 67–76, (2001). Available from <http://portal.acm.org>.
11. Szarfman A, Machado SG, O'Neill RT, Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Safety, 25(6): 381–92. (2002).

12. DuMouchel W, Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Statistician* X; 53: 177-190, (1999).
13. O'Neill RT, Szarfman A, Discussion: Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Statistician*, 53: 190–196. (1999).
14. Louis TA, Shen W, Discussion: Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Statistician*, 53: 196–198, (1999).
15. Madigan D, Discussion: Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Is Statistician*, 53: 198–200, (1999)?
16. DuMouchel W, Reply: Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Statistician*, 53: 201–202, (1999).
17. Gould L Practical Pharmacovigilance analysis strategies. *Pharmacoepidemiol Drug Safety*, 12: 559–574, (2003)
18. O'Neill RT, Szarfman A, Some FDA perspectives on data mining for pediatric safety assessment. *Workshop on adverse drug events in pediatrics, Curr Ther Res Clin Exp*, 62: 650–663, (2001).
19. Szarfman A, Tonning J. M. and Doraiswamy P. M. Pharmacovigilance in the 21st Century: New Systematic Tools for an Old Problem. *Pharmacotherapy*, 24: 1099–1104, (2004).
20. Philip Routledge, 150 years of Pharmacovigilance. *The Lancet*, 351,( 9110): 1200 - 1201,( 18 April 1998 ).
21. Ang- lee MK , Moss J, Yaan C, Herbal medicines and Perioperative care. *Journal of American medical association*, 286: 208-216, (2001)
22. Barnes J, Mills SY, Abbot NC, Willoughby M, Ernst E, 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*, 45(5):496-500. (May1998).
23. Thatte U, Bhalerao S, Pharmacovigilance of Ayurvedic medicines in India. *Indian journal of Pharmacology*, 40 (7):10-12, (2008).
24. Pon Gurusironmani, Siddha Toxicology, Department of Indian medicine and Homoeopathy, pg:64,70,72,78, First edition – August (1999).
25. Edwards IR, Aroson JK, Adverse drug reactions: Definitions, diagnosis and management. *The Lancet* 356:1255-1259, (2000).
26. Gagnier J, Boon H, Rochon P, Moher D, Barnes J, and Bombardier C, for the consort group, Controlled trials evaluating herbal interventions: Implementing the consort statement. *Drug safety*, 29: 911-1010, (2006).
27. Winslow LC, Kroll DJ, Herbs as medicines. *Archives of Internal medicine*, 158: 2192-2199, (1988). 23, 30. Gossell M, Simon OR, West ME, The past and present use of plants as medicines. *West Indian medical journal*, 55:217, (2006).
28. De-Smet PGAM, The role of plant derived drugs and herbal medicines in health care. *Drugs. International journal of pharmaceutical sciences and research*, 54:801-840, (2006).
29. Kinsel JF, Straus SE, Complementary and alternative therapeutics, rigorous search is needed to support claims. *Ann Rev Pharmacol Toxicol*, 289:43463-43484, (2003).
30. Ernst E, A primer of complementary and alternative Medicine commonly used by cancer patients. *Medical J Aust*174: 88-92, (2001).
31. Barnes J, Pharmacovigilance of herbal medicines: A UK perspective. *Drug safety*, 26: 829-851, (2003).
32. Kuh MA, Herbal remedies: Drug- herb interactions. *Critical care nurse*, 22: 22-32. (2002).
33. Animal, Pharmacovigilance of herbal medicines: An itangible approach. *IJPSR*, 1(11):60-65, (2010).
34. Shaw Debbie, Ladds Graeme, Duez Pierre, Williamson Elizabeth, Chan Kelvin, Pharmacovigilance of herbal medicine. *Journal of ethnopharmacology* 140:513-518, (2012).

35. Dr Xiaorui Zhang, WHO guidelines on safety monitoring of herbal medicines in Pharmacovigilance systems. World Health Organization, Geneva, (2004).
36. WHO Programme for International Drug Monitoring. Available from URL: www.who-umc.org on 29th (2009).
37. Pharmacovigilance an essential tool World Health Organization (2006).
38. Operational guidance: Information needed to support clinical trials of herbal products Lepakhin V. Geneva (2005).
39. Pirmohammed, M et al.. Adverse drug reactions as a cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 329: 15-19, (2004).
40. Lazarou J, Pomeranz BH, Corey PN, Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 279(15):1200-1205, (April 1998).
41. Shanthi paul , Quality assurance and safety of goods. The need for Pharmacovigilance (2009).
42. Pandi selvi A, Rajkumar S, Pharmacovigilance - A review. *Asian journal of pharmaceutical science and technology*, 2(2): 92-94, (2012).
43. Dineh Kumar Pandurangan, Ryali Jithedra, Bandrau Sowjana, Vijaya Rajkumar Perumal M, Pharmacovigilance-An overview. *IJRPS*, 2(2): 301-303, (2011).
44. Pipasha B, Arun Kb, Setting standards for proactive Pharmacovigilance in India: The way forward. *Indian j pharmacol*, 39(3):124-8, (2007).
45. Szarfman A, Tønning JM, Doraiswamy PM, Pharmacovigilance in the 21st century: New systematic tools for an old problem. *Pharmacotherapy*, 24(9):1099-1104, (SEP2004).
46. Meyboom RHB , Hekster YA, Egberts AC, Gribnac FWJ, Edwards IR, Casual or causal? The role of causality assessment in Pharmacovigilance. *Drug safety*, 16: 374-389, (1977)
47. Rahman, SZ; Khan, RA "Environmental pharmacology: A new discipline". *Indian J Pharmacol*. 38 (4): 229–230, (Dec 2006).
48. Rahman, SZ, Khan RA, Gupta V, Uddin, Misbah."Pharmacoenvironmentology – A Component of Pharmacovigilance". *Environmental Health* 6 (20): (July 2007).
49. Rahman SZ, Khan RA, Gupta V, and Misbah Uddin "Chapter 2: Pharmacoenvironmentology – Ahead of Pharmacovigilance". In Rahman SZ, Shahid M & Gupta A. *An Introduction to Environmental Pharmacology* 1st edn, Aligarh: Ibn Sina Academy. 35–52. (2008).
50. Ilene Sue Ruhoy, Christian G. Daughton, beyond the medicine cabinet: An analysis of where and why medications accumulate. *Environment International*, 34 (8): 1157-1169, (2008).
51. Janaki.R, Torvi, Rajesh Hunashal, Pharmacovigilance .*International Journal of Pharma and Bio Science* 2(4):95-102, (2011).
52. Sheetal Verma, S.P. Singh, Current and future status of herbal medicines .*Veterinary World*, 1(11): 347-350 (November 2008).
53. Unnikrishnan Payyappallimana, Role of Traditional Medicine in Primary Health Care: An Overview of Perspectives and Challenges. *World Health Report*, (2006).