

# Pharmacovigilance in Ayurveda: Statistical Input for Signal Detection



Arunabh Tripathi<sup>1</sup>, Rohit Sharma<sup>2</sup>, Achintya Mitra<sup>3</sup>, Rohit K Ravte<sup>4</sup>, Jayram Hazra<sup>5</sup>, T Saketh Ram<sup>6</sup>

## ABSTRACT

**Aim:** To review the intrinsic tenants available for safe drug usage in Ayurveda and to contextualize the statistical signal detection techniques of current times in terms of Ayurvedic pharmacovigilance program.

**Materials and methods:** Streamlining the information to develop a database that differentiates between known adverse drug reactions (ADRs) from hitherto unknown drug reactions per the standard definition of ADR. To introduce amicable statistical methods viz., Chi-square test, odds ratio (OR), and logistic regression for signal detection.

**Results and conclusion:** The proposed method of developing a known ADR and safe drug usage practices described in Ayurveda that followed the application of standard operating procedures for signal detection as per the pharmacovigilance program by applying statistical methods suggested will ensure pragmatic signal detection.

**Keywords:** Adverse drug reaction, Logistic regression, Pharmacovigilance, Signal detection.

*Journal of Drug Research in Ayurvedic Sciences* (2019): 10.5005/jdras-10059-0061

## INTRODUCTION

The aim of Ayurveda is twofold viz., protection of health in healthy individual and subsidence of morbidity in a sick person.<sup>1</sup> The holistic approach of Ayurveda toward healthcare of humans encompasses various aspects including safety and efficacy of substances used externally and internally as food, medicine, self-care, etc., among them the safety of drug usage is paramount; and time and again Ayurvedic texts emphasize on the aspect of safe usage of drugs/procedures by enlisting side effects/contraindications/complications (vyapad) alongside indications with respect to herbal/mineral/animal origin drugs as single entities or in combinations. For example, *Charaka Samhita* explicitly states that the science of life (Ayurveda) deals with substances that are life promoting (*Ayushyani*) and harmful to life (*Anayushyani*);<sup>2</sup> in the same text, the plausible complications (vyapad) arising out of therapeutic procedures viz., therapeutic emesis etc. and how one must be prepared to handle them are vividly discussed.<sup>3</sup>

According to the Confederation of Indian Industry, in the year 2016, the total estimated market size of Indian Ayurveda industry is US\$3 billion, which includes both Ayurveda products (ethical, classical, over-the-counter, personal care, and beauty products) and service (medical, well-being, payer, and medical tourism services).<sup>4</sup> Further, Ayurvedic pharmaceutical industry has an estimated number of 7,698 pharmacies out of which only 0.4% are managed by the government and the rest are managed by nongovernment bodies.<sup>5</sup> Although the entire process is highly regulated through D&C 1940 (Chapter IVA, Provisions related to Ayurveda, Siddha and Unani Drugs),<sup>6</sup> the data about safety and efficacy and safety of most of the patent and proprietary drugs licensed under Ayurveda are elusive. Further, there is also no mechanism in place of drug surveillance for these drugs after they are released into the market. On the contrary, information about *Shastric Drugs (generic)* based on the literature/narrative from accepted authoritative texts listed under the First Schedule of D&C 1940<sup>7</sup> have the advantage of track back system based on the textual narrative at least. In spite of this,

<sup>1,6</sup>National Institute of Indian Medical Heritage, Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Hyderabad, Telangana, India

<sup>2</sup>Department of Rasa Shastra and Bhaishajya Kalpana, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

<sup>3-5</sup>Central Ayurveda Research Institute for Drug Development, Kolkata, West Bengal, India

**Corresponding Author:** Arunabh Tripathi, National Institute of Indian Medical Heritage, Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Hyderabad, Telangana, India, Phone: +91 9506737515, e-mail: ashoka07b@yahoo.in

**How to cite this article:** Tripathi A, Sharma R, Mitra A, et al. Pharmacovigilance in Ayurveda: Statistical Input for Signal Detection. *J Drug Res Ayurvedic Sci* 2019;4(1):33–38.

**Source of support:** Nil

**Conflict of interest:** None

there is every possibility of unforeseen effects/adverse drug events while using this set of drugs.

Apart from this, unhealthy trends of use of Ayurvedic drugs directly by the patients as self-medication or erroneous prescriptions by registered Ayurveda<sup>8,9</sup> practitioners or in the form of cross pathy (use of synthetic/pure chemical-based drugs by Ayurveda physicians and use of single-/multi-ingredient medicines based on Ayurveda especially the patent and proprietary (P&P) category drugs by biomedical practitioners) are a potential zone for triggering unsafe drug usage and the possibility of unwarranted drug<sup>10,11</sup> reactions.

All these factors make it mandatory for us to apply the standard protocol set for pharmacovigilance of Ayurveda, Siddha, and Unani drugs.

Pharmacovigilance is a science for detection, assessment, and prevention of adverse drug reaction (ADR) in any system of<sup>11</sup> medicine. For a longtime, pharmacovigilance is being practiced in the context

of biomedicine. The World Health Organization (WHO) started this program and a number of countries of the world are being reported their ADRs, which arise due to the practice of allopathic medicine, where India is also one of them. Concerning with this issue, the Indian government also started a program for Ayurvedic pharmacovigilance for the betterment of Ayurvedic drug practice on global acceptance. This program has been running since 2010 in<sup>12</sup> India.

## SIGNAL

The main aim of any pharmacovigilance system is to find some new ADR from certain drugs, and this phenomenon is also known as signal.

### CLASSIC WHO DEFINITION OF "SIGNAL"

*"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information".<sup>13</sup>*

A signal is essentially a hypothesis of a risk with a medicine, with data and arguments that support it, data derived from one or more of many possible sources. The evidence in a signal is not conclusive (in the technical sense, uncertain) and is only an early indication (preliminary), as it may change substantially over time as more data accumulate.<sup>13</sup>

### Hauben and Aronson Definition

"Information that arises from one or multiple sources (including observation and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verifactory and, when necessary, remedial actions".<sup>14</sup>

The Council for International Organizations of Medical Sciences (CIOMS) VIII definition [adopted by European Medicines Agency (EMA)] is a slightly modified version of this, which is as follows:

"The definition of a signal as provided by the CIOMS working group 8 is: "... information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verifactory action".<sup>15</sup>

### Process of Signal<sup>16</sup> Management

The process of signal management in pharmacovigilance is a set of activities that aim to determine the new risks associated with a particular drug or whether risks associated with a particular drug have changed the sources for the detection of signals can come from:

- Spontaneous reporting
- Active monitoring systems
- Interventional studies (clinical trials)
- Noninterventional studies (pharmacoepidemiology studies)
- Nonclinical studies (e.g., animal toxicology studies)
- Systematic reviews (i.e., thorough review of the published literature)
- Meta-analyses (i.e., mathematical pooling of all the clinical trial data)
- Other relevant sources

### Examples of Signal Detection and Impact on Drug Prescription

Pharmacovigilance is beneficial for public health that avoids such medicine which shows serious ADR during practice. In allopathic pharmacovigilance, a number of signals are detected from its initiation, e.g., Stevens–Johnson syndrome due to paracetamol practices, valproic acid responsible for slurring of<sup>17</sup> speech.

In case of Ayurveda, the level of understanding about pharmacovigilance is dismal. Per the study conducted by Prakash et al., only 7% of Ayurveda physicians ( $n = 60$ ) participated in the study knew the definition of ADR and only 2% attempted to report some sort of ADR. Further, many of the participants, i.e., up to 75% do not know about the pharmacovigilance program meant for Ayurvedic drugs.<sup>18</sup> Further, till date notifications are available with respect to ADR in Ayurveda, Siddha, and Unani systems of medicine in India.

This situation calls for immediate attention for developing an appropriate signal detection and analysis system meant for Ayurveda and also Siddha and Unani drugs.

The first and foremost prerequisite for developing this system is to build a database of all classical and P&P formulations up to the granularity of single drugs and their properties (part- and formwise) along with toxic effects/side effects. Comprehensive work in this direction for classical preparation has been attempted by Council of Scientific and Industrial Research (CSIR)-Traditional Knowledge Digital Library (CSIR-TKDL).<sup>19</sup> However, per their policy currently the data are only accessible to the National Patent officers. In this scenario, it is prudent to pursue TKDL to provide access to authorized Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) officials, or the Ministry of AYUSH should consider developing its own independent database for this purpose. This will enable to cross check whether an ADR arising due to the use of certain Ayurveda, Siddha, Unani (A–S–U) drug is expected/documented already or is a completely new one, so that it can be considered as signal.

The database should be comprehensive and also have the rigor and schematic clarity as that of<sup>16</sup> Vigiflow, which is developed and maintained by Uppasala Monitoring Centre.<sup>20</sup> This is the standard reference database for all biomedical drugs across the world.

As of now in India two parallel PV programs are running, viz., (1) Pharmacovigilance Programme of India managed by the Indian Pharmacopoeial Commission, Ministry of Health and Family Welfare, Government of India, Ghaziabad.<sup>21</sup> (2) The National Pharmacovigilance Programme for Ayurveda, Siddha, Unani, and Homoeopathy Systems of medicine under the aegis of the Ministry of AYUSH, Government of India. Currently the All India Institute of Ayurveda (AIIA), New Delhi, has been designated as the National Pharmacovigilance Centre for this program.<sup>22</sup> In this case, the former is well equipped with enough manpower and expertise to collect, analyze, and report ADR. With respect to A–S–U, although the technical expertise collates the ADRs from all over the country, there seems to be a gap with reference to the application of appropriate statistical methods for efficient signal detection and notification. The scope of the paper is to suggest suitable statistical methods for the same.

### Statistical Methods of Signal Detection

The standard statistical methods utilized for signal detection are, viz., the empirical-based geometrical mean used by the US Food and Drug Administration; the information component (IC) value used by WHO; and the Chi-square test, OR, and logistic regression<sup>17,23–25</sup> Among them, the Chi-square test, OR, and logistic regression are quite appropriate for signal detection of Ayurveda drugs.

According to Ayurveda, the properties of śaṅkhaṣuṣpi are, viz., astringent taste (kaṣāya rasa), hotness (uṣṇa guna), having rejuvenating (rasāyana), memory improving (medhya), virilizing (vṛṣya), improving recall (smṛtikara), improving skin color (kāntiprada) and appetite, and enhancing the digestive capacity (agnibalakara); it is indicated to treat psychological ailments (mānasaroga), loss of memory/epilepsy (apasmāra) due to doṣa vitiation, skin ailments (kuṣṭha), worm infestation (krimi), and poisoning (viṣa).<sup>26</sup>

It is one of the widely marketed single-herb preparations in the name of Ayurveda and consumed by people of all age-groups and gender. This is also one of the widely studied herbs for herb–drug interaction especially with respect to decreased concentrations of phenytoin when combined with the Ayurvedic syrup sankhpuspi.<sup>27,28</sup> Keeping in view of the same, it becomes one of the best candidates to apply these statistical methods for understanding ADRs reported for this herb.

### Application of Chi-square

Chi-square is a well-known test for finding association between two categorical variables. The parameter degree of freedom for Chi-square test is determined by (Row-1)\*(Column-1). If one drug and one ADR is taken for the study, then the following 2\*2 Table 1 gives the layout of analysis. In case of multilevel of drug–ADR combination, the pattern of Table 1 becomes like 3\*3, 3\*2, 3\*4, 4\*2, etc., which can also be dealt with using multinomial distribution.<sup>29</sup> Chi-square test gives the statistical significance of association, which is also based on Chi-square distribution. According to the theory of Karl Pearson, Chi-square distribution may be used to test the agreement between observation and hypothesis whenever the data are in the form of frequency. Here the test concerns about two types of frequency, namely, one is the observed frequency and the other is the expected frequency. The observed frequency is the number of subject in our sample that fall in various categories of the variable of interest. Expected or theoretical frequencies are the number of subjects based on our hypothesis. The test statistic for Chi-square test is calculated as

$$\chi^2 = \sum \frac{(O_{ij} - E_{ij})^2}{E_{ij}}$$

where

$O_{ij}$  is the observed frequency of the cell in *i*th row and *j*th column

$E_{ij}$  is the expected frequency of the cell in *i*th row and *j*th column

On the basis of the above formula, we find Chi-square values and further *p* value will be found corresponding to the test values on the basis of Chi-square distribution with degree of freedom (Row 1)\*(Column 1).

**Table 1:** One drug dose and ADR combination layout

|       | ADR+         | ADR–         | Total                |
|-------|--------------|--------------|----------------------|
| Drug+ | <i>a</i>     | <i>b</i>     | <i>a + b</i>         |
| Drug– | <i>c</i>     | <i>d</i>     | <i>c + d</i>         |
| Total | <i>a + c</i> | <i>b + d</i> | <i>a + b + c + d</i> |

Drug (+), no. of people exposed to drug; Drug (–), no. of people unexposed to drug; ADR (+), no. of people experienced ADR; ADR (–), no. of people not experienced ADR

The scope of Chi-square test is limited to the identification of relationship between the drug and ADR. This test will not assess the strength of association.<sup>30</sup>

Hence, to find the strength of association, it is necessary to take certain statistical measure of association, which is fit in prescribed data structure, viz., relative risk and OR. Relative risk can be considered only in case of incident data, i.e., if a group of people is treated by certain drug from the same starting point of time and followed up to the same time limit. In pharmacovigilance, the data collection pattern does not follow this culture. So OR is a better choice. Odds ratio is the ratio of two odds.<sup>31,32</sup>

### Application of Odd Ratio

Odds are defined by probability of occurrence of certain event/probability of certain event not occurring. If  $p_1$  is the probability of occurrence of ADR in the drug-exposed group and  $p_2$  is the probability of occurrence of ADR in the drug not exposed group. Then  $p_1 = a/(a + b)$ , similarly  $p_2 = c/(c + d)$ , then the odds for ADR for the drug-exposed group is

$$\frac{p_1}{1-p_1} = \frac{a/(a+b)}{b/(a+b)} = a/b$$

Similarly the ADR odds for the drug not exposed group is

$$\frac{p_2}{1-p_2} = \frac{c/(c+d)}{d/(c+d)} = c/d$$

As in Table 1, the ADR odds when a drug had been taken is  $a/b$ , and the ADR odds ADR when a drug had not been taken is  $c/d$ , then the ADR OR when drug has been taken to the ADR odds when drug had not been taken is

$$OR = \frac{\frac{p_1}{1-p_1}}{\frac{p_2}{1-p_2}} = (a/b)/(c/d) = \frac{ad}{bc}$$

To find the confidence interval (CI) of OR, it is necessary to know the distribution of OR. But the actual distribution of OR is not tractable; however, the logarithm (at base *e*) of it has been found to be approximately normal; by this the standard error (SE) of log (OR) is calculated using the following formula

$$SE[\text{Log(OR)}] = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

With the standard format of CI (  $\text{Log(OR)} \pm 1.96 * SE[\text{Log(OR)}]$  ), 95% CI can be calculated. By taking the anti-log of the above quantities, the original CI of OR can be calculated.

### Application of Regression Analysis

Suppose multiple drugs are given to a patient and certain ADR is raised, then identifying the drug that is responsible for the ADR or interaction of the drugs is responsible for ADR, is the concern of the pharmacovigilance system. Simple statistical methods as discussed in earlier paragraph cannot cope with this question. The answers of these questions can be drawn by regression<sup>33,34</sup> analysis; the concept and technique of regression analysis for analyzing the association among several variables are natural extension of the above-mentioned techniques. In multiple regression analysis, a linear relationship exists between dependent and independent

variables. In pharmacovigilance, the dependent variable is ADR and the independent variable is the various drugs given to the patient. According to the data pattern (e.g., nominal, ordinal, or continuous) of the dependent variable, different types of regression analyses are used. The dependent variables is ADR, namely, ADR present or ADR absent, i.e., it involves only two possible outcomes. In such situation, logistic regression analysis will be carried out to find the effect of each drug in the presence of other drugs. The interaction effect can also be found.

Suppose P is the probability of an ADR event occurring. If three drug such as  $x_1$ ,  $x_2$ , and  $x_3$  were simultaneously given to the patients, then the following setup is used for the analysis:

$$\begin{aligned} \text{Log} \left[ \frac{P}{1-P} \right] &= \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3 \\ \frac{P}{1-P} &= e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3} \\ P &= \frac{e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3}}{1 + e^{\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3}} \end{aligned}$$

where  $\beta_1, \beta_2$ , and  $\beta_3$  are the regression coefficients for independent drug effects of  $x_1, x_2$ , and  $x_3$ .  $\beta_{12}$  gives the interaction effects of drugs  $x_1$  and  $x_2$ . Similar interpretation for  $\beta_{13}, \beta_{23}$ , and  $\beta_{123}$  gives the interaction effect of drugs  $x_1, x_2$ , and  $x_3$ .

Per the description of  $p_1$  and  $p_2$  in OR, suppose  $x_1$  is the concern drug. To calculate the OR according to logistic regression methodology when the concern drug is present,  $x_1 = 1$

$$\begin{aligned} \frac{p_1}{1-p_1} &= e^{\beta_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3} \\ \frac{p_1}{1-p_1} &= e^{\beta_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3} \end{aligned}$$

And when the concern drug is absent,  $x_1 = 0$

$$\begin{aligned} \frac{p_2}{1-p_2} &= e^{\beta_1 \cdot 0 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3} \\ \frac{p_2}{1-p_2} &= e^{\beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3} \end{aligned}$$

$$\text{It implies that OR} = \frac{e^{\beta_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3}}{e^{\beta_2 x_2 + \beta_3 x_3 + \beta_{12} x_1 x_2 + \beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3}} = e^{\beta_1}$$

It gives  $\text{Log (OR)} = \beta_1$

It describes that the odds of ADR in drug  $x_1$  given category  $e^{\beta_1}$  times are higher as compared to the odds of drug  $x_1$  without the given category, where the remaining variables/drugs are at constant level. Similarly other regression coefficient and OR can be defined.

The multi-ingredients, viz., haridra (*Curcuma longa*)-rhizome powder (1–3 g), amalaki (*Phyllanthus emblica*) fresh juice (10–15 mL), and chandraprabha vati (250–500 mg), a well-known combination for the management of madhumeha (diabetes mellitus),<sup>35</sup> can be a model to understand the plausible ADR in multicomination treatment. Though this combination is very safe in usual parlance, at times there may be instances of uncontrolled blood glucose levels and minor side effects (ADR) such as dryness of skin, itch, rashes, etc. One question arises here, i.e., whether the ADR caused by either any drug or the interaction effect of drugs. The answer to this question cannot be given by using the 2\*2 platform as discussed

earlier. The answer to the above question can be given by using logistic regression analysis.

The above-mentioned methods are described in classical setup of statistics. In classical setup of statistics, the current data are considered to describe the situation. Another inference procedure in statistics is Bayesian inference procedure.<sup>36</sup> It not only deals with current situation but also considers the previous status of phenomena. This approach is more mathematical, but it can enhance the capacity of researcher to detect a<sup>23,24</sup> signal by incorporating the previous information.

## CONCLUSION

The pharmacovigilance program intended for Ayurveda under the aegis of the AIIA, New Delhi, states the purpose of the initiative in the following lines: "The common 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. Hence, AYUSH practitioners and consumers now need to be vigilant about the safety monitoring of drugs in the interest of public health." In tune with the spirit of the objective, the paper attempts to review the current status of pharmacovigilance program with respect to Ayurveda. As per the published literature, it can be concluded that as of now the understanding about this subject is very dismal at this stage. Researchers from pharmacovigilance field<sup>9,11</sup> opine that, it is not easy to find the role of Ayurvedic medicine in certain ADRs. This warrants for the need to sensitize Ayurveda Vaidyas and other stakeholders to be vigilant and report ADRs diligently to the scientific community. Further, it is also observed that there is a dire need of developing a comprehensive database of Ayurveda drugs with already known pharmacotherapeutic effects, indications, contraindications, precautions for use, etc., similar to the Vigiflow, so that any unpredictable/hitherto unknown arising from the use of particular Ayurvedic drug can be properly detected and the signal can be further tracked. To achieve this objective, the system has to be supported with robust statistical methods viz., Chi-square test, OR, and logistic regression in consonance with safe Ayurvedic drug use tenants to facilitate pragmatic signal detections and further notification of the same per the necessity.

## REFERENCES

1. Krishnamurthy KH. A source book of Indian medicine: an anthology. B.R. Pub. Corp; 1991. p. 2, 9.
2. Krishnamurthy KH. A source book of Indian medicine: an anthology. B.R. Pub. Corp; 1991. p. 8.
3. Krishnamurthy KH. A source book of Indian medicine: an anthology. B.R. Pub. Corp; 1991. p. 67.
4. Ayurveda Industry Market Size, Strength and Way Forward [Internet]. 2018 [cited 2019 Mar 22]. Available from: www.cii.in. p. 5.
5. Ayurveda Industry Market Size, Strength and Way Forward [Internet]. 2018 [cited 2019 Mar 22]. Available from: www.cii.in. p. 19.
6. Government of India Ministry of Health and Family Welfare (Department of Health). The Drugs and Cosmetics Act and Rules. The Drugs and Cosmetics Act, 1940 (23 of 1940). The Drugs and Cosmetics Rules, 1945 List of Abbreviations Used [Internet]. [Cited 2019 Mar 28]. Available from: <http://www.cdsc.noic.in/writereaddata/Drugs&CosmeticAct.pdf>. p. 19.
7. Government of India Ministry of Health and Family Welfare (Department of Health). The Drugs and Cosmetics Act and Rules.

- The Drugs and Cosmetics Act, 1940 (23 of 1940). The Drugs and Cosmetics Rules, 1945 List of Abbreviations Used [Internet]. [cited 2019 Mar 28]. Available from: <http://www.cdsc.nic.in/writereaddata/Drugs&CosmeticAct.pdf>. p. 1, 27.
8. Edwards RI, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *The Lancet* 2000;356(9237):1255–1259. DOI: 10.1016/S0140-6736(00)02799-9.
  9. Ajanal M, Nayak S, Prasa BS, et al. Adverse drug reaction and concepts of drug safety in ayurveda: an overview. *J Young Pharm* 2013;5(4):116–120. DOI: 10.1016/j.jyp.2013.10.001.
  10. Chaudhary A, Singh N, Kumar N. Pharmacovigilance, boon for the safety and efficacy of ayurvedic formulations. *J Ayurveda Integr Med* 2010;1(4):251–256. DOI: 10.4103/0975-9476.74427.
  11. Thatte U, Bhalerao S. Pharmacovigilance of Ayurvedic medicines in India. *Indian J Pharmacol* 2008;40(Suppl 1):S10–S12.
  12. National pharmacovigilance programme for Ayurveda Sidha and Unani Drugs - 2008 (Protocol).
  13. Delamothe T. Reporting adverse drug reactions. *Br Med J* 1992;304:465. Available from [<https://www.who-umc.org/research-scientific-development/signal-detection/what-is-a-signal/>].
  14. Hauben M, Aronson JK. Defining 'Signal' and its subtypes in pharmacovigilance based on a systematic review of previous definitions. *Drug Saf* 2009;32(2):99–110. DOI: 10.2165/00002018-200932020-00003.
  15. Online Available from [<https://www.primevigilance.com/resources/complexities-drug-safety/signal-detection-in-pharmacovigilance/>].
  16. Online Available from <https://adr.who-umc.org/container.asp?sSessionId=&sPage=>.
  17. Kalaiselvan V, Tripathi A, Saurabh A, et al. Quantitative methods for identification of signals for individual case safety reports in India. *Ther Innov Regul Sci* 2015;49(2):898–902.
  18. Prakash BG, R SK, Chandra Reddy VK, et al. Knowledge, attitude, and practice of pharmacovigilance among ayurvedic practitioners: a questionnaire survey in Andhra Pradesh, India. *Natl J Physiol Pharm Pharmacol* [Internet] 2016. Available from: [www.njppp.com](http://www.njppp.com).
  19. TKDL Traditional Knowledge Digital Library [Internet]. Available from: <http://www.tkd.l.res.in/tkd.l/langdefault/common/Home.asp?GL=Eng>.
  20. UMC | Uppsala Monitoring Centre [Internet]. Available from: <https://www.who-umc.org/>.
  21. Pharmacovigilance Programme of India [Internet]. Available from: <https://ipc.gov.in/PvPI/about.html>.
  22. Pharmacovigilance - All India Institute of Ayurveda, New Delhi [Internet]. Available from: <https://aiia.gov.in/pharmacovigilance/>.
  23. Ranjan A, Tripathi A, Saurabh A, et al. Signal detection in pharmacovigilance: an application of subjective Bayesian inference. *Adv Pharmacoepidemiol Drug Saf* 2016;5:207.
  24. Madigan D, Ryan P, Simpson S, et al. Bayesian methods in pharmacovigilance. *Bayesian Statistics* 2010;9:1–17.
  25. Suling M, Pigeot I. Signal detection and monitoring based on longitudinal healthcare data, pharmaceuticals. 2012;4(4):607–640.
  26. Bhavaprakasha Prathamkhanda, Mishrakavarga, Guducyadivarga/228, accessed from e-nighantu, [niimh.nic.in](http://niimh.nic.in).
  27. Kshirsagar NA, Dalvi SS, Joshi MV, et al. Phenytoin and ayurvedic preparations: clinically important interaction in epileptic patients. *J Assoc Physicians India* 1992;40(5):354–355.
  28. Dandekar UP, Chandra RS, Dalvi SS, et al. Analysis of a clinically important interaction between phenytoin and Shankhapushpi, an ayurvedic preparation. *J Ethnopharmacol* 1992;35(3):285–288. DOI: 10.1016/0378-8741(92)90026-N.
  29. Johnson K, Guo C, Gosink M, et al. Multinomial modelling and an evaluation of common data mining algorithms for identifying signals of disproportionate Reporting in pharmacovigilance database. *Bioinformatics* 2012;28(23):3123–3130. DOI: 10.1093/bioinformatics/bts576.
  30. Agresti A. *Categorical Data Analysis*. John Wiley & Sons; 2002. pp. 34–35.
  31. Agresti A. *Categorical Data Analysis*. John Wiley & Sons; 2002. pp. 28–31.
  32. Armitage P, Berry G, Matthews JNS. *Stat Methods Med Res*. Blackwell Science Publishing; 2002. pp. 671–675.
  33. Agresti A. *Categorical Data Analysis*. John Wiley & Sons; 2002. pp. 65–90.
  34. Armitage P, Berry G, Matthews JNS. *Stat Methods Med Res*. Blackwell Science Publishing; 2002. pp. 187–204.
  35. [http://www.ccras.nic.in/sites/default/files/Guidelines\\_for\\_prevention\\_and\\_management\\_of\\_Diabetes.pdf](http://www.ccras.nic.in/sites/default/files/Guidelines_for_prevention_and_management_of_Diabetes.pdf).
  36. Armitage P, Berry G, Matthews JNS. *Stat Methods Med Res*. Blackwell Science Publishing; 2002. pp. 165–183.

## हिंदी सारांश

आयुर्वेद में फ़ार्माकोविजिलेंस: सिग्नल डिटेक्शन हेतु सांख्यिकीय इनपुट

**उद्देश्य:** आयुर्वेद में सुरक्षित औषध प्रयोग हेतु उपलब्ध वास्तविक हितधारकों की समीक्षा करना और आयुर्वेदिक फ़ार्माकोविजिलेंस कार्यक्रम के संदर्भ में वर्तमान समय में सांख्यिकीय सिग्नल डिटेक्शन तकनीकों को प्रासंगिक बनाना।

**सामग्री और विधियां:** एक डाटाबेस विकसित करने हेतु एडीआर की मानक परिभाषा के अनुसार ज्ञात प्रतिकूल औषध प्रतिक्रिया (एडीआर) से अब तक अज्ञात औषध प्रतिक्रियाओं के बीच अन्तर करना ताकि सूचना को मुख्यधारा में लाया जा सके। परस्पर-संगत सिग्नल डिटेक्शन हेतु सांख्यिकीय पद्धतियों यथा काई-स्क्वायर परीक्षण, ओड्स रेशियो (ओआर) और लोजिस्टिक रिग्रेशन को लाना।

**परिणाम और निष्कर्ष:** सुझाए गई सांख्यिकीय पद्धतियों द्वारा फ़ार्माकोविजिलेंस कार्यक्रम के अनुसार सिग्नल डिटेक्शन हेतु आयुर्वेद में वर्णित ज्ञात एडीआर और सुरक्षित औषध प्रयोग प्रक्रियाओं हेतु मानक संचालन प्रक्रिया के प्रयोग को विकसित करने के लिए प्रस्तावित प्रणाली व्यावहारिक सिग्नल डिटेक्शन को सुनिश्चित करेगी।

**मुख्य शब्द:** प्रतिकूल औषध प्रतिक्रिया, लोजिस्टिक रिग्रेशन, फ़ार्माकोविजिलेंस, सिग्नल डिटेक्शन।

