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Pharmacovigilance of Herbal Drugs: AComprehensive Review

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ABSTRACT
When it comes to herb-drug interactions and herbal therapy, pharmacovigilance is crucial. Clinical studies and case reports have reported numerous herb-drug interactions; drugs with a narrow safety margin include amitriptyline, digoxin, cyclosporine, warfarin, and tacrolimus. Because of their potential and growing cost, herbal medicines are becoming more and more significant in pharmacovigilance systems. They do, however, carry some concerns, such as the possibility of adverse responses. Long-term carcinogenicity testing, toxicity research, and patient-specific studies ought to be included in safety reviews. The health of a patient may suffer from modest to severe consequences as a result of herb-drug interactions. Given that herb-drug interactions are more common than drug-drug interactions, pharmacovigilance is essential for recognising, assessing, understanding, and preventing adverse effects or problems related to medications.

KEYWORDS: Pharmacovigilance, Herbal Drug, adverse event, herb-drug interaction, regulation, clinical trials.

I. INTRODUCTION

The creation of reliable information about the safety of drugs that are on the market in the context of clinical use in society. Expanding safety monitoring and identifying drug-unidentified adverse events that were assessed in clinical trials but were not previously known are the goals. Nevertheless, these approaches were designed to monitor pharmaceutical drugs; they are also applied to assessments of the safety of other drugs, like herbal medicines, blood products, vaccines, and medical supplies [1].The World Health Organisation (WHO) established guidelines for the supervision of herbal safety under the "The WHO guidelines on safety monitoring of herbal medicines under the existing pharmacovigilance framework systems for pharmacovigilance" in response to the growing importance of herbal medicines in the world [2].

The fact that 67.6% of people use herbal medicine globally attests to the significance of these traditions. Natural remedies have been employed in the US. Over 158 million Americans spent a total of US$ 17 billion. (2000) [3]. Based on information from 3027 respondents, it was estimated that 52.1% of South Australians who had reported at least in 2000 had visited at least one herbal practitioner. Of all respondents, 23.3% said they had done so [4].More than 70% of respondents to a recent German poll claimed to utilise "alternative medicines," with herbal remedies being the go-to treatment for the majority of minor illnesses. For primary healthcare, almost 80% of the world's developing population turns on traditional medicine [3]. Results from research conducted in Nigeria indicate that there is insufficient supervision of the negative effects observed by practitioners and emphasise the need to inform and familiarise practitioners of herbal medicine with the requirements of pharmacovigilance for herbal products [5].

PHARMACOVIGILANCE IN HERBAL DRUGS

"The detection, assessment, and understanding of the prevention of drug-related problems or adverse effects at therapeutic concentrations that are used or are intended to be used to modify or explore physiological system or pathological states for the benefit of recipient" is the definition of pharmacovigilance as given by the World Health Organisation. A WHO research states that 70% of people worldwide receive treatment for a range of disorders from traditional medical systems, and traditional medicine is widely recognised internationally [11].The majority of side effects associated with these herbal remedies are caused by either inadequate or incorrect product use.The fundamental reasons of these unfavourable events are believed to be a deficient quality control system, an inadequate regulatory framework, and mostly unregulated distribution methods[12].

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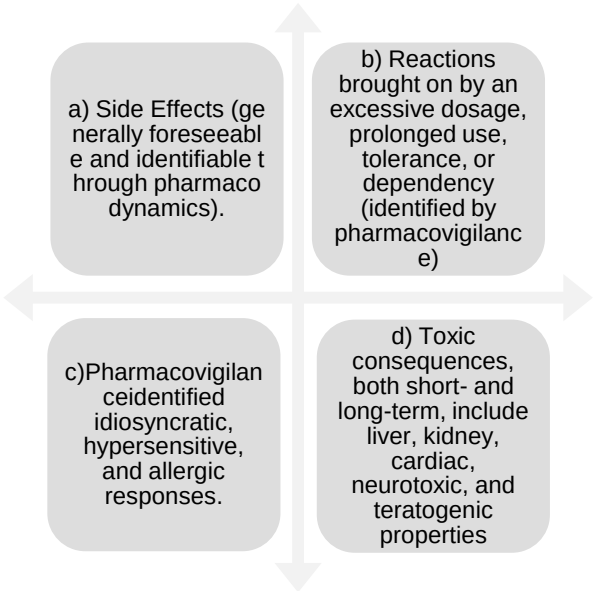

Fig.1.0 - Unfavourable outcomes of herbal drugs

The prevalence of quality issues with Unani herbal products, such as mislabeled or misidentified plants, inadequate processing methods, and the supply of contaminated or adulterated herbs or products, has made pharmacovigilance an important part of this process. The World Health Organisation (WHO) has applauded and encouraged the proactive involvement of multiple stakeholders in global drug regulation, including multiple Pharmacovigilance Centres, in creating appropriate recommendations for the entire process. In India, the Ministry of AYUSH has taken a step in this direction by implementing Pharmacovigilance systems for various traditional herbal medicine systems, such as Ayurvedic, Sidda, and Unani (ASU), and by considering WHO recommendations about the safety of herbal medicines [13]. An international initiative led by the World Health Organisation (WHO) has provided a centralised platform for improving communication across different alternative systems and ensuring progress towards a common goal, which is the safety of herbal treatments. The developed policy has led to the inclusion of herbal pharmaceuticals in the National Pharmacovigilance System [14]. The National Pharmacovigilance System was established with the goal of identifying the challenges associated with effectively monitoring the safety of herbal medicines and formulating suitable countermeasures. Reporting negative reactions to herbal medicines used in the Unani System and looking into the causes of those reactions were the main priorities [15].

METHODS OF PHARMACOVIGILANCE FOR HERBAL DRUGS

Pharmacovigilance for Herbal Drugs include active surveillance, such as conducting post-marketing studies and monitoring adverse drug reactions reported by healthcare professionals and patients. Another method is passive surveillance, which involves collecting and analysing spontaneous reports of adverse events from healthcare professionals and consumers. These methods help to identify any potential safety concerns associated with herbal medicines and enable regulatory authorities to take appropriate actions to protect public health [28, 29]. Scholars and pharmaceutical businesses operating in China also endeavour to detect safety signals through various datasets, including clinical study findings, the Healthcare Information System, and health insurance databases. The intricacies and peculiarities of keeping an eye on the safety of H&TMs are seldom taken into account by pharmacovigilance procedures and instruments created within the framework of traditional medicine [30]. Approaches must be modified in light of particular H&TM challenges, such as those involving H&TM quality, labelling, and the usage of botanical nomenclature. SRSs (Spontaneous reporting system) should be used to gather safety data as part of continuous pharmacovigilance programs, and they should be well constructed in

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order to more accurately represent real-world treatment environments, post marketing studies (PMSs).

Detecting Signals from SRSs and the Medical Literature

Pharmaceutical companies, medical experts, and consumers report suspected adverse reactions to the national center of regulatory authorities, and SRSs are frequently used to monitor and detect drug safety signals. Globally, national pharmacovigilance centers send those reports to VigiBase, the WHO Collaborating Center for Monitoring Drug Safety, Uppsala Monitoring Center [UMC], Global Individual Case Safety Report (ICSR) Database. The UMC has overseen the main functions of the growing global pharmacovigilance network since 1978. As of the end of April 2017, the network comprised 154 countries, or 95% of the world's population, with both full and associate members. This network is known as the WHO Programme for International Drug Monitoring, and it contained more than 15 million ICSRs in the VigiBase. The UMC was forced to deal with nomenclature concerns since it receives herbal reports from nations that have various TM (Traditional Medicines) systems which led to the creation of an ICSR database for herbal products [32, 33] and a Herbal Anatomical Therapeutic Chemical (HATC) classification system [31]. Herb–adverse event pairs that are reported at disproportionate rates are found using quantitative approaches, and this can help find safety signals in VigiBase and national pharmacovigilance center datasets [34]. Pharmacovigilance is better known nationally thanks to signal detection activities [35].

Role of spontaneous reporting, observational studies, and systematic reviews in monitoring herbal drug safety

Spontaneous reporting is a crucial part of active surveillance, allowing healthcare professionals and patients to report adverse effects or reactions associated with herbal drugs. This data is then analyzed to identify potential safety concerns. Observational studies provide in-depth information on real-world use and outcomes of herbal drugs in large populations. Systematic reviews synthesize findings from multiple studies to provide a comprehensive overview of the safety profile of herbal drugs. This helps healthcare professionals make evidence-based decisions and identify gaps in knowledge.

Adverse Events and Reporting

One challenge in identifying and reporting adverse events related to herbal medicines is the lack of standardized reporting systems. Unlike pharmaceutical drugs, there is no universal system in place for healthcare professionals to report adverse events specifically related to herbal drugs. This can make it difficult to gather comprehensive data on the frequency and severity of these events. Additionally, there may be underreporting of adverse events due to a lack of awareness or reluctance among healthcare professionals and patients to attribute symptoms or complications to herbal drug use. Plants and plant material are used to promote healing and maintain health-related issues in herbal medications. The practice of using herbal remedies became popular in Egypt back in 1550 BC [36]. Approximately 80% of people on the planet utilize herbal remedies and products related to herbs. The use of herbal remedies is growing daily as people become more trusting of natural goods and want to avoid the harmful effects of chemicals; each year, this usage rises at a rate of 10-15% [37]. Because most herbal medications are self-prescribed and used to treat a wide range of ailments, including both acute and chronic health issues, it is imperative that they be safe. The majority of patients who take herbal remedies are unaware of its potential. There could be negative consequences from these preparations. They are ignorant of the risks associated with the ingredients in herbs. There are now more side effects associated with herbal remedies than growing in the pharmacovigilance research. The number of cases of adverse effects caused by herbal drugs has also increased as a result of greater herbal use and, most likely, higher consumer and clinical practitioner awareness [38]. Due to growing awareness of the harm that industrialization and its chemicals inflict to the environment, there is a movement toward using goods made of natural substances [39]. Herbal supplements gained popularity after consumers of other drugs and chemicals reported experiencing multiple negative effects [40]. 60% of conventional medications sold worldwide, whether directly or indirectly, come from natural sources, such as herbs [41]. This misconception is reinforced by numerous other unfounded assertions, such as the idea that conventional medications have chemicals in them while herbal products do not, which adds to the side effects of the latter. Numerous examples of herbal medicine reactions have been reported, owing to doctors' awareness of pharmacovigilance analysis [42,43].

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HERB–DRUG INTERACTION

Few studies that have been done in which herb-drug interaction has shown some changes in the pharmacokinetics as well as pharmacodynamics of the drugs are given below:

Ephedra + antidepressants	Elevated blood pressure/ heart rate
Garlic + ginger + Warfarin	Increase bleeding
Carica papaya (extract) + Warfarin	increase international normalised ratio (INR)
Liquorice + oral contra captive	increased hypersensitivity
Liquorice + Digoxin	increased effect of cardiac glycoside
Tamarind + aspirin	increased bioavailability of aspirin
Jujube + indomethacin	increased bioavailability of indomethacin
Psoralia seed + tetracyclin	causes photo allergy

Fig. 1.1 – Herb-Drug interactions

II. DISCUSSION

The use of herbal drugs has skyrocketed recently on a global scale [44]. The primary justification for this is the conviction that it promotes healthy living and causes no negative side effects. People hold these beliefs about herbal medication as a result of poor labelling, insufficient quality control, and incorrect information [45]. Because it is more difficult to evaluate herbal goods than conventional medicines, it has become crucial for consumers and healthcare professionals to be aware of pharmacovigilance problems with adverse effects and herbal drugs [46,47]. Following the revelation of some cases of multiple follicular formation linked to herbal therapy, pharmacovigilance of herbal drugs became more important [48]. Fessenden and associates did a case report on bleeding following a laparoscopic cholecystectomy and the use of herbal medicine [49].

RISK-BENEFIT ASSESSMENT

Over the past decade, the use of herbal remedies and products has increased globally, raising concerns about potential interactions with traditional medication therapy. The herbal-drug interface (HDI) is the main therapeutic outcome of this strategy, with evidence based on a formal assessment technique. Phytochemicals, active compounds found in herbal products, can interact with prescription medications, altering their effectiveness or increasing the risk of side effects. Therefore, healthcare professionals should be aware of potential HDIs and patients should disclose their use of herbal products when seeking medical advice or treatment. Further research is needed to fully understand the mechanisms and clinical implications of HDIs to ensure the safe and effective use of both herbal and conventional medications.

Importance of conducting risk-benefit assessments in pharmacovigilance

Risk-benefit assessments are crucial in pharmacovigilance to evaluate the safety and efficacy of medications, including herbal products. These assessments help healthcare professionals make informed decisions about the appropriate use of these products, considering potential interactions and individual patient factors. By prioritizing patient safety and optimizing treatment outcomes, these assessments contribute to improving the quality of healthcare delivery. They help manage adverse events and prevent harm to patients, while also providing valuable data for enhancing regulatory policies and guidelines. This promotes patient trust in the healthcare system and fosters a culture of patient-cantered care.

HERBAL DRUGS AND THEIR ASSOCIATED PHARMACOVIGILANCE ISSUES

Despite efforts to encourage reporting of herbal adverse drug reactions (ADRs), the number of herbal ADR reports received by regulatory bodies remains low. This underreporting is expected to be severe due to users often not seeking professional advice or disclosing unwanted effects. Insufficient quality control, weak regulatory supervision, and uncontrolled distribution are factors contributing to this issue. To increase the safety of herbal medicines globally, regulatory bodies must address botanical identification, herb traceability, ecological issues, over-the-counter herbal medications, and barriers between patients

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and physicians. The lack of standardized reporting systems and challenges in herbal traceability pose risks to consumer safety and undermine the credibility of herbal medicines, ensuring authenticity and purity.

The identification of adverse reactions requires pharmacovigilance, as many herbal drugs on the market have not undergone extensive testing to confirm their effects on pharmacology and toxicology [50,51]. The World Health Organization launched the International Drug Monitoring Program, with participation from over 70 member states, to evaluate adverse occurrences linked to herbal remedies. Nonetheless, the adverse effects of these herbal remedies as recorded by various countries were infrequent. Moreover, effective communication on this matter is lacking on all fronts, from the international to the local. A recent WHO study indicates that almost 90 countries control herbal goods. Fewer of these nations have laws governing or approving vendors of natural medicines.

Furthermore, there are notable variations in country laws, which adversely affect the international distribution and accessibility of these goods [52].

III. FUTURE DIRECTIONS AND RECOMMENDATIONS

In the future, a robust PV (pharmacovigilance) system that can identify new adverse drug reactions and put regulatory measures in place to safeguard the public's health will be required. There hasn't been much focus on the development of data that can help a patient or healthcare professional make a decision. The main goal of pharmacovigilance is to gather and disseminate this data. Information regarding the security of drug-active surveillance is essential [54]. Going forward, PV systems will need to concentrate on using patients as a source of information in addition to more conventional groups like medical professionals. Good Pharmacovigilance Practice (GPP) should be included in processes and procedures by the DCGI as soon as possible to improve PV and increase clinical trial safety, post-marketing surveillance, and regulatory compliance. A functional photovoltaic system is necessary for the safe usage of medications. It will be advantageous to consumers, pharmaceutical companies, regulatory agencies, and healthcare professionals [53]. Given the abundance of clinical trials and other clinical research endeavours occurring in India, it is imperative to comprehend the significance of pharmacovigilance and its impact on the product life cycle. A lot of effort has been made by DCGI to develop a pharmacovigilance system that is dependable and efficient. To fulfil the needs of a growing population and make sure that all data is gathered and processed, greater effort and strategic planning are needed. The DCGI may go ahead and hire private companies to train and set up an efficient pharmacovigilance system in order to address the challenges of inexperience and a shortage of trained personnel [55].

Taking into account the challenges and barriers India faces in creating a successful pharmacovigilance system, the following recommendations could be made:

1. Setting up and keeping up a strong system of pharmacovigilance.
2. Implementing PV inspections and requiring the reporting of them.
3. High-level conversations with diverse stakeholders.
4. Increase the number of medical and scientific experts with training who assess PV at the Drug Control General of India office.
5. Developing a single adverse event reporting form that everyone, wherever in the world, can use.
6. Ensure that every pharmaceutical business has a consistent database where they can keep track of all new drugs and indications.
7. Pharmacovigilance education and training are provided to nurses, pharmacists, and medical students.
8. Working together with pharmacovigilance organizations to enhance drug safety: As information technology develops, new opportunities for international and national cooperation to enhance postmarking surveillance programs have surfaced.

IV. CONCLUSION

Healthcare systems have historically relied on natural materials from plants, animals, and minerals. Ethnomedicine systems like Ayurveda, Siddha, Unani, Kampo, TCM, Muti, Ifa´, and Islamic medicine have potential for developing novel agents. Today, 25% of drugs have active properties from plants. Pharmacovigilance is crucial for preventing drug-related problems. Traditional medicine, used by 70% of people worldwide, has been linked to toxicity and negative reactions due to improper usage, subpar products, and inadequate regulatory frameworks. The safety of herbal remedies is a major concern for regulatory bodies due to adverse effects like

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hepatotoxicity, renal failure, and carcinogenicity. To ensure safe use, international bodies must address their guiding principles and develop a unified regulatory framework for herbal remedies and supplements. Active and passive monitoring techniques are used in pharmacovigilance for herbal medications in order to spot possible safety issues and give regulatory bodies the information they need to take the necessary precautions to safeguard the public's health. While passive surveillance gathers and examines unplanned adverse events, active surveillance entails post-marketing research and the observation of adverse medication reactions.

The importance of continued vigilance in ensuring the safety of herbal drugs. The lack of defined reporting mechanisms for herbal medicines poses a challenge in identifying and reporting adverse events, as there is no standardized mechanism for reporting these occurrences. This can lead to underreporting of adverse events, as patients and healthcare providers may be hesitant or unaware of the link between herbal drug use. Healthcare professionals and patients should be aware of herbal products' potential for herbal drug interface, and further research is needed to understand their mechanisms and clinical implications. Regulatory organizations face low reports of adverse drug reactions with herbal medicines due to insufficient quality control, monitoring, and unregulated distribution. Addressing over-the-counter herbal treatments, patient-physician conflicts, ecological issues, botanical identification, and herb traceability is crucial. A robust pharmacovigilance system is needed to identify adverse drug reactions and implement regulatory measures. The main goal is to gather and disseminate data, ensuring drug-active surveillance security. PV should focus on patients and medical professionals, and Good Pharmacovigilance Practice (GPP) should be included in processes. A functional photovoltaic system is necessary for safe medication usage, benefiting consumers, pharmaceutical companies, regulatory agencies, and healthcare professionals. DCGI has made efforts to develop a reliable and efficient system, but more strategic planning is needed to meet the growing population's needs.

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