PHARMACOVIGILANCE IN HERBAL INDUSTRY: ENSURING SAFETY AND EFFICACY OF TRADITIONAL MEDICINES

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➢ **ABSTRACT :**

Herbal medicine has grown rapidly in recent years, with 80% of people in undeveloped countries still relying on traditional plant-based medicine for primary health care. Over 500 therapeutic effects have been documented in ancient literature, and around 800 herbs are used in traditional medicine. The need for new herbal products with therapeutic benefits is growing as more people seek natural remedies. Pharmacovigilance in India began in 1986 with an Adverse Drug Reactions (ADR) monitoring system, which failed. In 2005, India's WHO-funded National Pharmacovigilance Programme (NPPV) was launched. PV collects, monitors, and evaluates information from healthcare providers and patients on the adverse effects of medications, biological products, blood products, herbals, vaccines, medical devices, and complementary medicines to identify hazards and prevent harm to patients. The regulatory landscape surrounding Pharmacovigilance has undergone significant transformation, with international collaboration efforts harmonizing requirements across different regions. The COVID-19 pandemic has placed unprecedented pressure on Pharmacovigilance systems, with stakeholders including regulatory authorities, pharmaceutical companies, healthcare professionals, and patients playing crucial roles in the effective functioning of Pharmacovigilance systems.

➢ **Keywords:** Pharmacovigilance, Herb-Drug interaction, WHO Guidelines, Research and future directions.

➢ INTRODUCTION :

Herbal medicine has grown at an exponential rate in recent years, with approximately 80% of people in undeveloped countries still depending on traditional plant-based medicine for primary health care. More than 500 therapeutic effects of traditional medicine have been documented in ancient literature. Approximately 800 herbs are used in traditional medicine. The need for new herbal products with therapeutic benefits is growing as more people look for natural remedies; these products need to be further developed and supported by science.(1,2) The World Health Organization (WHO). defines herbal medicines as finished, branded pharmaceutical preparations that comprise active ingredients, aerial or subterranean plant parts, or other plant material or mixes.(3) Herbal medicines have been used by many groups and civilizations worldwide since the Palaeolithic era. The number of people utilizing over-the-counter herbal drugs has grown during the last few decades. Herbal medicines have been widely accepted as therapeutic agents, including adaptogens; cough remedies, hepatoprotectives, anti-diabetics, anti-arthritics, and aphrodisiacs. They are typically regarded as safe because they come from natural sources. (4) Pharmacovigilance in India started from 1986. A formal Adverse Drug Reactions (ADR) monitoring system was established with 12 regional centres, each serving a population of 50 million. However, no significant growth was achieved. In 1997, India attempted to join the World Health Organization (WHO) and the Adverse Drug Reaction (ADR) monitoring program based in Uppsala, Sweden, but was unsuccessful. As a result, after 2005, the WHO-supported and World Bank-funded National Pharmacovigilance Programme (NPPV) of India was activated.(5) PV is the science of gathering, monitoring, researching, assessing, and evaluating information from healthcare providers and patients about the adverse effects of medications, biological products, blood products, herbals, vaccines, medical devices, and traditional and complementary medicines in order to find new information about product hazards and prevent patient harm. The task of maximizing drug safety while preserving public trust has grown increasingly difficult. Drug risk must be actively estimated and managed by pharmaceutical and biotechnology businesses at every stage of a product's lifecycle, from development to post-market. (6) The regulatory landscape surrounding Pharmacovigilance has also undergone significant transformation, with international collaboration efforts such as the International Council for Harmonisation (ICH) harmonizing the regulatory requirements for Pharmacovigilance across different regions. Key guidelines like ICH E2E on Pharmacovigilance planning and ICH E2F on periodic benefit-risk evaluation reports (PBRER) have brought consistency and a unified approach to drug safety monitoring. The role of regulatory bodies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the World Health Organization (WHO) has expanded to include rigorous post-marketing surveillance requirements, risk management strategies, and proactive Pharmacovigilance systems. (7) Pharmacovigilance has become even more critical in the current era of rapid technological and therapeutic innovation. The development of complex biological therapies, including monoclonal antibodies, gene therapies, and personalized medicine, presents new challenges for Pharmacovigilance systems that were initially designed to monitor traditional small-molecule drugs.

As treatment complexity rises, there is a greater need for specific techniques to safety monitoring. Additionally, the emergence of global health crises such as the COVID-19 pandemic has placed unprecedented pressure on Pharmacovigilance systems, particularly in the context of the accelerated development and emergency use of vaccines and treatments.(8) The current Pharmacovigilance landscape is multifaceted, involving a wide array of stakeholders, including regulatory authorities, pharmaceutical companies, healthcare professionals, and patients. Every one of these categories is essential to the efficient operation of Pharmacovigilance systems. Healthcare workers and patients contribute by reporting adverse events, whereas pharmaceutical corporations are responsible for constant safety monitoring and regulatory compliance. Regulatory authorities, in turn, oversee the entire process, ensuring that drug safety data is rigorously evaluated and that necessary actions, such as labelling changes, risk mitigation strategies, or product withdrawals, are implemented to protect public health.(9)

PHARMACOVIGILANCE :

Pharmacovigilance, a French term referring to identifying side effects of drugs, their treatment, documentation, reportage, and regulatory decisions based on them, is a well-established science in the developed world Pharmacovigilance is the pharmaceutical science concerned with the identification, assessment, understanding, and prevention of adverse effects or other drug-related issues, notably long-term and short-term side effects of medications. Pharmacovigilance is the science of gathering, monitoring, investigating, assessing, and evaluating information from healthcare providers and patients about the side effects of drugs, biological products, herbalism, and traditional therapies. (10)

➢ **OBJECTIVES :**

❖ Pharmacovigilance strives to monitor adverse effects from lab to pharmacy, improve public health and safety, encourage safe and cost-effective drug usage, and educate on Pharmacovigilance practices and training, and communicate effectively with the public.
❖ Pharmacovigilance studies aim to inform consumers, practitioners, and regulators on drug efficacy, as well as develop mechanisms for collecting and analysing patient and clinician reports.(11)
❖ Improvement of patient care and safety in relation to the use of medicines with medical and paramedical interventions remains to be an important parameter.(12)
❖ Providing consumers, practitioners, and regulators with effective information use of drugs along with designing programs and procedures for collecting and analysing reports from patients and clinicians conclude to the objectives of Pharmacovigilance studies.(12,13)

➢ **NEEDS :**

❖ It is widely accepted that clinical development of medicines is a complex process which also includes herbal drugs and their products. Once a drug is marketed, it leaves the secure and protected scientific environment of clinical trials and is free for consumption by the general public. At this point, most herbal medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals.(14)
❖ Hence, need of Pharmacovigilance in herbal drugs arises which include, securing the early detection of new adverse reactions or patients subgroups of exceptional sensitivity; and introducing certain measures in order to manage such risks.
❖ Moreover, it is essential that new and medically still evolving treatments are monitored for their effectiveness and safety under real-life conditions after being marketed.
❖ Furthermore, more information is generally needed about use in specific population groups like children, pregnant women and the elderly, about the efficacy and safety of chronic use in combination with other drugs.(15)

➢ **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:

Fig. 1.1 – Herb-Drug interactions (16)

Herb +drugs	**Effects**
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

➢ WHO GUIDELINES FOR HERBAL DRUG INTERACTIONS :

The World Health Organization (WHO) has issued recommendations for dealing with HDIs to improve the safety and efficacy of medical therapies that combine herbal treatments alongside conventional medications. These recommendations emphasize how important it is for medical practitioners to comprehend the pharmacokinetic and pharmacodynamics interactions that may occur when herbal medicine are taken with prescription drugs. Because herbal ingredients affect the enzymes and transporters that break down drugs, pharmacokinetic interactions can change how drugs are absorbed, distributed, metabolized, or excreted. On the other hand, pharmacodynamics interactions take place when herbs use comparable biological pathways to either increase or decrease the therapeutic effects of medications. WHO urges medical professionals to ask patients about all supplements they may be taking and stresses the value of informing patients about possible HDIs? To efficiently monitor side effects and interactions, the guidelines also support the incorporation of herbal remedies into current Pharmacovigilance systems. WHO also urges greater research to better understand the mechanisms behind HDIs, which are still a poorly understood field of pharmacology? The ultimate objective is to improve patient outcomes in contemporary healthcare settings by giving medical practitioners all the materials they need to make educated decisions and guarantee secure simultaneous utilization of traditional and herbal medications. (17,18)

➢ PHARMACOVIGILANCE IN DRUG REGULATION :

Pharmacovigilance and all drug safety issues are relevant for everyone whose life is touched in any way by medical interventions. Robust drug regulatory arrangements provide the foundation for a national ethos of drug safety, and for public confidence in medicines. The issues, with which drug regulatory authorities have to contend besides the approval of new medicines, include:

- clinical trials
- safety of complementary and traditional medicines, vaccines and biological medicines
- Developing lines of communication between all parties with an interest in drug safety and ensuring that they are open and able to function efficiently, particularly at times of crisis.

Pharmacovigilance programmes need strong links with regulators to ensure that authorities are well briefed on safety issues in everyday practice that may be relevant to future regulatory action. Regulators understand that Pharmacovigilance plays a specialized and pivotal role in ensuring on going safety of medicinal products. Pharmacovigilance programmes need to be adequately supported to achieve their objectives. A new medicine must pass three hurdles before its approval by the national drug regulatory authority. Sufficient evidence is required to show the new drug to be Safe for the purpose or purposes for which it is proposed. (19)

➢ Drugs used in various ailments :

- **Garlic (*Allium sativum*):**

Garlic mainly contains organosulfur compounds such asallicin, diallyl disulphide, diallyl trisulphide and S-allyl cysteine. Garlic is used as antihyperlipidemic. Antimicrobial, anti-inflammatory, anti-protozoal, anti-cancer and immune modulatory activity. Garlic has been reported to show toxicity at higher doses. In contrast, some studies also showed intoxication after consumption of garlic.(20) Clinical study shows that the intake of S-allyl cysteine (active constituent of garlic) inhibits platelet aggregation. (21) Inhibition of platelet aggregation shows an additive anticoagulant effect, which is a possible mechanism for warfarin and garlic interaction, which ultimately increases the anticoagulant effect. Increased anticoagulant may increase the risk of bleeding. (22) The pre-supplementation and post-supplementation effect of garlic on CYP2E1 enzyme was evaluated by measuring 6-

hydroxychlorzoxazone/chlorzoxazone serum ratio. A controlled trial showed a decrease in 6-hydroxychlorazoxazone/ chlorzoxazone serum ratio by about 22%, which suggests inhibition of CYP2E1 activity by garlic (23)

- **Green tea *(Camellia sinesis)* :**

Green tea mainly contains catechins, polyphenols and epigallocatechin-3-gallate. Green tea possesses antioxidant, antimutagenic, ant diabetic, anti-inflammatory, antibacterial and antiviral properties. Green tea is used for weight loss and preventing ageing and prostate and other cancers. (24) An in vivo study reported that catechins (present in green tea extract) inhibit folic acid uptake. Catechins are competitive inhibitors of DHFR, which adversely affect folate uptake. DHFR is responsible for folate intestinal Surana et al. Future Journal of Pharmaceutical Sciences (2021) 7:103 Page 5 of 12absorption. Folate is reduced to tetrahydrofolate and methylated to 5-methyltetrahydrofolate during intestinal absorption of folate before it is absorbed in the blood. (25) A clinical trial in humans reported that green tea weakly inhibits CYP450 3A4, which is the main metabolizing enzyme of simvastatin. (26)

- **Gingko *(Ginkgo biloba)*:**

Ginkgo biloba leaf contains flavonol glycosides (kaempferol, quercetin, myricetin, apigenin, isorhamnetin, luteolin and tamarixetin) and terpene trilactones (ginkgolide A, B, C, J, K, L, M, P, and Q and bilobalide), proanthocyanidins and organic acids. G. biloba leaf extract is used in the treatment of Alzheimer's disease, neurodegenerative disease, cerebral insufficiency, neurosensory problems, eye ailments, vascular insufficiencies, age-related memory deficit and oxidative stress. In addition, G. biloba is leaf used as anti-angiogenesis, anti-inflammatory, and anti-asthmatic. (27) In a case study, fatal seizures were reported with anticonvulsant medications like valproic acid. GBE has been reported to induce CYP2C19 enzyme activity. The CYP450 enzyme is reported to metabolise valproate, chiefly by CYP2C9 and CYP2C19. Thus, this coadministration of valproic acid and Ginkgo biloba extract should be prevented. (28)

- **Liquorice *(Glycyrrhizin glabra)*:**

Biologically active compounds present in liquorice are glycosides (glycyrrhizic acid), flavonoids (chaconnes, liquiritin, isoliquiritin, liquiritin apioside and isoprenoid-substituted flavonoids), chromenes (coumarins and dihydrostilbenes) and saponins (triterpenoid saponins). Liquorice is reported for wide-ranging biological activities like antiviral, anti-microbial, anti-oxidant, anti-allergic, hepatoprotective, neuroprotective, antiInflammatory and dermatological activities. (29) Glycyrrhizin induces CYP3A4 enzyme (which catalyses midazolam 11-hydroxylation), leading to a reduction in plasma concentrations of midazolam. Inhibition was confirmed by an *in vivo* study, where mRNA expression of CYP3A4 and other. (30)

- **St. John's wort *(Hypericum perforatum)*:**

St. John's wort is used as an antidepressant, antiviral and antibacterial. It also shows sedative and astringent properties. It is used traditionally for the treatment of excitability, neuralgia, sciatica, fibrosis, anxiety, menopausal neurosis and depression and as a nerve tonic and topical application for wound treatment. (31) The study confirmed that long-term use of SJW may cause reduced clinical effectiveness of CPY3A4 substrate drugs by CPY3A4 induction, which may lead to an increase in dosage of the drug. (32) Serotonin reuptake is weakly inhibited by SJW. Various reports of SJW interacting with SSRIs have been reported, leading to various side effects, including serotonin syndrome. The side effect is due to an additive effect of two similarly acting drugs. (33)

➢ RISK FACTORS :

HDIs are a major problem in modern healthcare, especially as the utilization of herbal remedies grows alongside traditional therapies. The pharmacological qualities of both herbal remedies and traditional medicines, particular to the patient attributes, including the potency of the herbal formulations alone are some of the factors that increase the risk of adverse reactions. A significant risk element is an individual's overall wellness. People who are experiencing comorbidity or individuals upon several drugs are more likely to acquire HDIs. Genetic variations can also affect the metabolism for both herbal and traditional drugs, compounding the effects of these interactions. (34) Herbal medications' pharmacokinetic and pharmacodynamics features are crucial when analysing HDIs. Most herbal items can inhibit the function of drug-metabolizing enzymes, specifically those in the cytochrome P450 family, resulting in changed drug concentrations in the body. For example, certain herbs can activate or block those enzymes, which results in either decreased efficacy or the increased toxicity of traditional medicines. The potential for adverse interactions is increased when active ingredients in herbal remedies collaborate with protein carriers which help with drug absorption and excretion. (35, 36) HDIs relate to a variety of risk parameters, including pharmacological features, product quality,

patient preferences, and the requirement for standard assessment techniques. Since incorporating herbal remedies into contemporary medical regimens is becoming more and more popular, it is imperative that these factors be taken into consideration to ensure patient safety. (34)

➢ RESEARCH AND FUTURE DIRECTIONS :

HDIs studies are becoming more vital in modern healthcare due to the increased usage of herbal supplements in conjunction with conventional pharmaceuticals. There is a high risk of negative interactions since users frequently self-administer these medications without telling their medical professionals. The body of current literature highlights the need for more thorough study, especially through observational studies that make use of -world data, to comprehend the therapeutic implications of HDIs. Because of ethical considerations and the Intricacy of herbal formulations, observational studies, for instance, might shed light on the prevalence and effects of HDIs in routine clinical settings, which are frequently missed in standard Randomized controlled trials (RCTs). (37) Subsequent investigations ought to concentrate on formulating uniform approaches for evaluating HDIs, encompassing sophisticated computer models that forecast interactions predicated on the pharmacokinetic characteristics of the plant components. Furthermore, by utilizing cutting-edge study designs like case-control as well as cohort studies, we can improve our comprehension about these interactions and their practical consequences. (38)

➢ CONCLUSION:

Pharmacovigilance plays crucial role in the herbal industry by ensuring the safety, efficacy, and quality of the herbal product.it helps in identifying and monitoring adverse drug reaction, assessing risk factors, and ensuring compliance with regulatory standards. As herbal medicine continuous to grow in popularity, robust Pharmacovigilance practices are essential to protect public health, mitigate potential risks, and provide accurate information to both consumers and health care professionals. On-going research and advancements in Pharmacovigilance will further enhance the ability to monitor and manage the safety of herbal products, ultimately guiding the industry towards safer, more effective therapeutic solutions.

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