REVIEW ARTICLE

The Importance of Pharmacovigilance in the Polyherbal Sector: Challenges and Future Potential

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ABSTRACT

Pharmacovigilance is crucial in ensuring the safety and potency of polyherbal products, as many have not been extensively evaluated for their pharmacology and toxicity. With the increasing popularity of polyherbal medications, there has been a rise in complaints of probable toxicity and adverse outcomes. This study investigates the importance of pharmacovigilance in the polyherbal sector and examines its challenges and future potential. Data was collected from various databases from 2000-2024. Pharmacovigilance has become a key domain in medicine and public health, with a significant portion of India's population relying on Indian medical systems. The study highlights the importance of implementing pharmacovigilance procedures for polyherbal medications, promoting rational use and appropriate treatment methods. Polyherbal drugs may have negative interactions with other medications, foods, biologicals, and compounds, leading to decreased therapeutic efficacy, undesirable side effects, and severe complications. Systematic pharmacovigilance is necessary to collect accurate data and develop guidelines for safe and effective use.

Keywords: Pharmacovigilance, Polyherbal, Safety, Individualized medicine, Interaction, Adverse event, quality.

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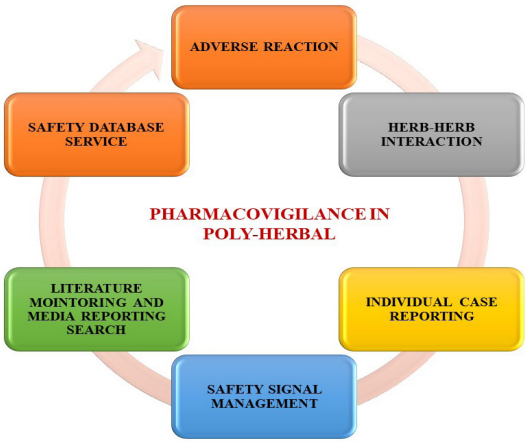

Graphical abstract

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]

Plants or plant parts are the basis of herbal medicines, which are used to treat illnesses injuries, and to encourage recovery. It is a medication or preparation intended for any of these uses that is made from one or more plants. The oldest form of medicine in the world is herbal medicine. The World Health Organization (WHO).[3] defines herbal medicines as finished, branded pharmaceutical preparations that comprise active ingredients, aerial or subterranean plant parts, or other plant material or mixes. The World Health Organization has established precise recommendations for evaluating herbal medication safety, efficacy, and quality. According to the WHO, around 81% of the world's population currently uses herbal medicine for basic care.[4] Natural products accounted for approximately half of all new drugs approved between 1995 and 2006. Between 2006 and 2008, drug authorities

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approved 13 natural product-based drugs, illustrating the importance of plant/natural resources in the drug development process. Butler *et al.* investigated 100 natural products and natural product-derived compounds in clinical trials, as well as 33 antibody-drug conjugates in clinical studies with a natural product-derived cytotoxic agent and a number of natural products in cancer clinical trial.[5] The discovery of vincristine from *Catharanthus roseus* flowers in the 1950s and paclitaxel from *Taxus brevifolia* bark in 1967 demonstrated the importance of plants in anticancer medication development.[6,7] To prevent and cure systemic illnesses, several pharmacological medicines were previously produced from natural materials. The compounds presently under development target a broad spectrum of indications, encompassing bacterial, viral, fungal, and parasitic infections; in addition, they target other therapeutic domains such as depression, neurological disorders, and cardiovascular diseases, as well as metabolic diseases like diabetes, cholesterol regulation, and inflammatory diseases.[8]

Polyherbal formulations are those that restrict the use of two or more herbs. Because of its medicinal and therapeutic properties, polyherbal formulations have been utilized all over the world. Polyherbal treatment or herb-herb combination is another name for it. Individual plant active phytochemical components are insufficient to provide the desired therapeutic effects. When polyherbal and herbo-mineral compositions combine numerous herbs in a precise ratio, the medicinal impact is boosted while toxicity is reduced. Individual plant active components are insufficient to create appealing pharmacological activity. There is evidence that crude plant extracts, rather than separated ingredients, have a higher efficacy. Rather than isolated chemicals, entire plants or mixes of plants are employed in traditional medicine. Due to synergism, polyherbal offers various benefits not seen in single herbal compositions. At large dosages, polyherbal formulations have shown remarkable efficiency in a number of ailments while being both safe and effective. Depending on the nature of the interaction, synergism can occur in two ways (pharmacodynamics and pharmacokinetics). Pharmacokinetic synergism refers to a herb's capacity to aid in the absorption, distribution, metabolism, and elimination of other herbs. Pharmacodynamic synergism, on the other hand, looks at the synergistic effects of active ingredients that have similar therapeutic efficacy but distinct modes of action.[9] When compared to a single medicine, drug combinations typically have a promising impact on the treatment of disorders. The notion of medication combination is well-established in Western medicine, and it has had a lot of success over the years. Drug combination therapy for cancer and infectious disorders has given patients fresh hope in recent years. The possible interaction effects of naturally occurring herbs and herbal substances grouped into a formula have been demonstrated. Mutual augmentation, mutual aid, mutual constraint, and mutual hostility are examples of these.[10,11]

The anticipated or predicted market for pharmaceuticals and pharmaceutical goods in 2022 is $1.12 trillion, indicating a growing global need for these items. The risk of infection and illness acquisition has grown as a result of changes in lifestyle, eating preferences, and environmental changes/pollution among the worldwide population.[12] The WHO promotes the use of traditional medicine to satisfy the healthcare requirements of the worldwide population since it is economical, safe, and culturally acceptable. In the preceding century, synthetic drug research altered the healthcare system, but the number of adverse events associated with medication, which is one of the leading causes of death, has also grown. In Africa, traditional medicine is used by up to 90% of the population, while in India, it is used by up to 70% of the population, as shown in Figure 1. In China, computers are installed in 90% of ordinary hospitals.[13] This sort of medical therapy has its origins in China and India. The connections between the body and the environment are at the heart of traditional Chinese medicine. The origins of traditional Indian medicine may be traced back to 3000 BC. Ayurveda was one type of traditional Indian medicine.[14]

Herbs have been used as a medicinal agent in traditional medical institutions for a long time. In the United States, traditional medicine is utilized by 38% of adults and 12% of children. Traditional remedies are used for a variety of reasons, including affordability, strict conformity with the patient's worldview, and easing of concerns about synthetic prescription adverse effects.[15] In the current context, there is a growth in the worldwide population of various pharmacological chemicals. There is also an increase in natural medications. Changes in environmental circumstances may lead to a reduction in biodiversity, resulting in an increase in the number of sensitive plants. The International Union for Conservation of Nature (IUCN) red list has over 79,800 species, with over 23,000 of them classified as endangered with extinction. We described the issues with polyherbal, the relevance of polyherbal, the present perspective, obstacles, and its value in pharmacovigilance, as well as its prospects in this review study.[16]

Pharmacovigilance and Polyherbal Formulation

The study and practice of identifying, analyzing, understanding, and preventing harmful medication effects and other drug-related difficulties is known as pharmacovigilance. Herbals, traditional and complementary treatments, blood products, biologicals, medical gadgets, and vaccinations have all lately been added to the list of things to be concerned about.[17] Pharmacovigilance has developed and will continue to change in response to specific demands and based on the unique capabilities of WHO Programme participants and other stakeholders. Such active influence should be embraced and encouraged; it is a source of vibrancy and creativity that has had a significant impact on global practice and standards.[18] There is a trade-off between the benefits and the potential for damage with all drugs. To reduce the risk of damage, it is critical that high-quality, safe, and effective medications are used sensibly and that the patient's expectations and concerns are considered when treatment decisions are made. To do this, it is necessary to promote public health by encouraging patients

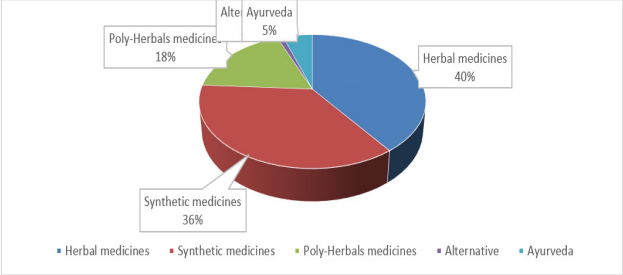

Figure 1: Use of different medicines in India

to have faith in the medications they take, which will eventually lead to trust in the health system as a whole. Since the WHO technical report in 1972, pharmacovigilance has undergone substantial evolution in response to the growing diversity and potency of drugs. Utilizing medications by licensed healthcare professionals and people who comprehend their prescriptions is essential to lowering the possibility of injury. It is crucial to properly assess and discuss toxicity and adverse effects, particularly for previously unidentified substances.

Concerns about the safety of herbal and traditional treatments have been raised. There is a widespread misperception that "natural" equates to "safe." Long-term usage of a drug, based on tradition, is thought to guarantee both efficacy and safety. Allopathic drugs, chemicals such as corticosteroids, non-steroidal anti-inflammatory agents, and heavy metals have been found to be adulterated or contaminated with traditional and herbal treatments.[19] Many traditional medicines are now produced for worldwide use, and they are no longer limited to the traditional and cultural contexts in which they were developed. Patients' risks are exacerbated by self-medication and, especially in the case of polyherbal, here is more risk of major adverse drug interactions, herb-herb interaction and polyherbal remedies are used with other medications. Polyherbal and herbal medicines' participation in national pharmacovigilance programs has become critical and unavoidable.[20] Traditional healthcare practitioners, regulators, manufacturers, and the general public all share responsibilities for their educated and safe usage. Guidelines for evaluating the safety, effectiveness, and quality of herbal medicines have been developed by the World Health Organization. The development of new systematic ways to evaluate the safety of plant-derived medical products is underway.[21] There are several challenges that must be overcome during the preparation of polyherbal medications, as shown in Figures 2 and 3.

Advantages of Polyherbal Over the Single herb

Herbal drugs, on the whole, have fewer unintended side effects than pharmaceutical drugs, so they are considered safer to use. Herbal medicines are less expensive than pharmaceutical medicines. Herbal medications are less expensive than allopathic pharmaceuticals because they are more accessible and cost-effective. These benefits of plant-derived medications can be used to justify their use as appropriate lead molecules for future drug development modification. The various architectures and intricate carbon skeletons of natural goods

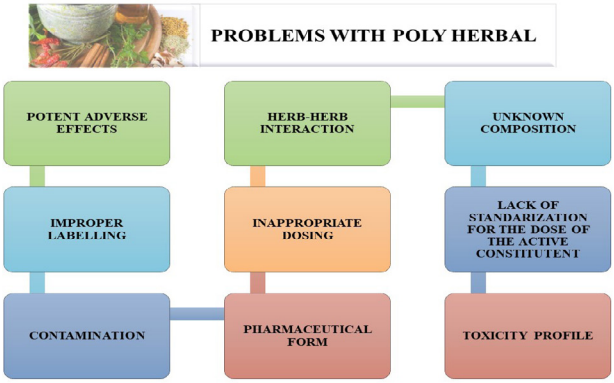

Figure 2: Problems with polyherbal: Several obstacles arise during the preparation of polyherbal preparations, and these parameters require specific consideration since they play a key role in the medication safety profile

have resulted in a substantial fraction of natural products being used in drug development. Secondary metabolites derived from natural sources are more biologically friendly.[22]

The multiple ingredients included in polyherbal formulations have a synergistic impact. Our forefathers used a combination therapy in which the herbs counteract each other's poisonous effects. If a single plant is used to treat a specific condition, the disease-causing agent may become resistant, but in the case of polyherbal formulations, the disease-causing pathogen is less likely to become resistant so that it can be successful for a long period, as the fact that the same ayurvedic formulas were used over 1500 years ago and are still effective now. Multiple active ingredients may be present in a medicament. The active ingredients in the polyherbal mixture work together in a synergistic way. As a result, the optimum polyherbal combination has a stronger anti-disease activity. Due to symbiosis, polyherbalism provides a number of benefits not seen in single herbal preparations. It is obvious that a single multi-constituent formulation can have a better therapeutic effect. A smaller dose of the herbal product would be necessary to produce the desired pharmacological action, reducing the risk of adverse side effects. PHFs can improve patient convenience by decreasing the need to take many herbal formulations at once, resulting in higher compliance and therapeutic impact. All of these benefits, when compared to single herbal formulations, have contributed to PHF's success on the market.

Polyherbal preparations, including different compounds, can provide comprehensive therapy for a range of ailments and problems. In order to lessen toxicity, adverse effects, bad taste, enhance color, create synergy, increase solubility, and cure a variety of ailments, including malnutrition, immunity, and physical weakness, these compositions combine many herbs.[23]

Adverse Drug Reactions

Polynatural remedies may not come without side effects. Polyherbal consists of two or many herbs, which means any herb can show its side effects. They can also have a range of negative consequences, from minor to severe.

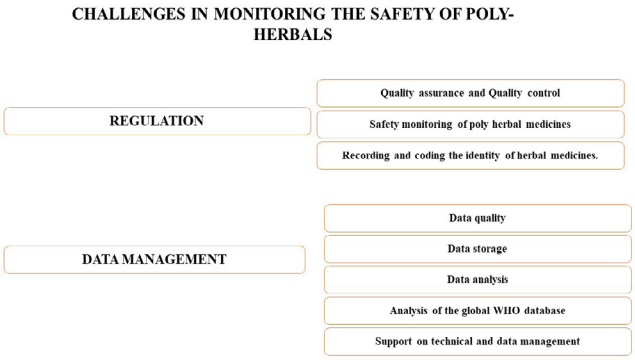

Figure 3: various challenges in monitoring the safety of polyherbal

Gastrointestinal disturbances, allergic reactions, lethargy, dizziness, photosensitivity, disorientation, hypertension, cardiac arrhythmias, myocardial infarction, anxiety, headache, and diarrhea are some of the most prevalent ADR.[24]

The possible interaction effects of naturally occurring herbs and herbal substances grouped into a formula have been demonstrated. Mutual augmentation, mutual aid, mutual constraint, and mutual hostility are examples of these.[25] Some examples of adverse effect of herbs are flaxseed (*Linum usitatissimum)* should not be used with laxatives or stool softeners since the laxative effect may be amplified. Feverfew *(Tanacetum parthenium)* is an herb with anti-inflammatory qualities that is commonly used to reduce the frequency and severity of migraine headaches. People who are sensitive to ragweed should avoid feverfew because it is a member of the daisy family. Ginger *(Zingiber officinale)* has been used and assessed as an antinauseant and antispasmodic agent with great effectiveness. Ginger slows bleeding because it inhibits thromboxane synthase. As a result, anyone taking warfarin or other medications that affect platelet activity should avoid taking ginger pills. The usage of ginger as a spice is not a problem. Kava *(Piper methysticum)* relieves anxiety, discomfort, and stress without decreasing alertness. Because kava is a dopamine antagonist, it can produce tremors and make Parkinson's disease medications less effective. Because kava potentiates alcohol, tranquilizers, and antidepressants, they should not be used simultaneously. Table 1 lists some of the most prevalent herbs and their harmful effects in detail.

Table 1: Common interaction of herbal drugs along with examples

S. No.	*Common type of interaction of natural drugs*	*Examples*
1.	Herb-herb interaction	• Piper betel + *Garcinia Morella* • *Basella alba* + *Sesamum indicum* • Glycyrrhiza roots + *Euphorbia pokinensis* root • Aconite + *Bletilla Striata* rhizome • Liquorice + Seaweed
2.	Herb-food interaction	• Redish + Milk • Equal quantity of Madhu + Grutha. • Sesame Seeds + Black cumin. • Shilajatu + Kakmachi. • Asafoetida + Honey. • Garlic + Milk. • Kampillaka + Buttermilk. • Bhallataka + Hot Water. • Kakmachi + Honey • Boswellia may interact with foodstuffs.
3.	Herb animal origin drug interaction	• Meat of Pigeon + *Brassica alba* • Pork + Oil of *Coccus nucifera* • Honey + Ghee
4.	Drug disease interaction	• *Terminalia chebula* contraindicated in Pregnancy • Papaya is contraindicated in pregnancy. • Tweak may interfere with conventional antidiabetic drugs • Aloe vera (Kumari) may interact with drugs which having blood-glucose-lowering properties. • Ashwagandha may affect digoxin and interfere with thyroid hormone. • Ephedrine may interact with steroids.
5.	Miscellaneous	• Idiosyncrasy • Drug-activity (exercise) Interaction

Herb-Herb Interaction

Herb-drug interactions are a major issue of discussion, and herbs are increasingly being criticized for posing a risk to patients who are already on prescription pharmaceuticals. Patients who are taking many drugs, typically recommended by various physicians who may or may not be in communication with one another about their medical reasons, have even more cause for concern. Non-accidental side effects of pharmaceuticals are the fourth greatest cause of mortality in the United States (106,000 fatalities per year), but yearly deaths from herbs were only a few in the United States until 2002.[26] When preparing a number of co-prescriptions, a particular notion of herb-herb interaction is used. Although each herb in a prescription is suggested for a specific symptom, when many herbs are combined, the combination becomes more than a random collection of herbs.[27] For thousands of years, the concept and practice of herb-herb combination has been acknowledged in medicine. When viewed from a scientific standpoint, the logic for multi-item prescriptions appears to be fabricated, yet their empirical benefits are undeniable. While the particular pharmacological processes are unknown, they are likely to entail pharmacokinetic, pharmacodynamic, and/or polyvalent effects.

Safety as a Fundamental Principle

The first harmonized program of pharmacovigilance was Resolution WHA23.13 on international monitoring of adverse reactions to drugs, which was adopted in 1970 as a result of collaboration between the WHO Collaborating Centre in Sweden and the Uppsala Monitoring Centre (UMC) as part of the International Drug Monitoring Program.[28] To reconcile

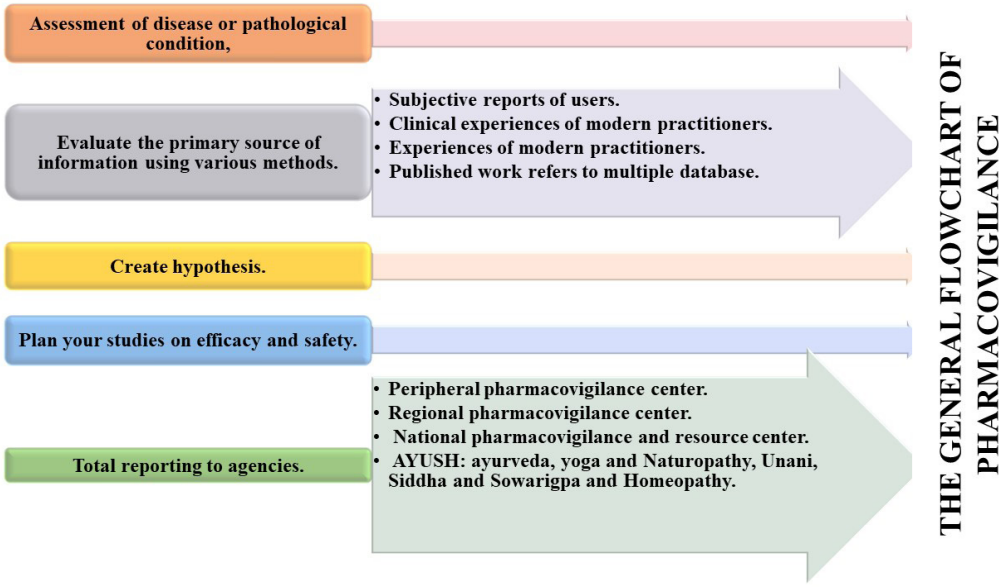

Figure 4: Study design for polyherbal

contradictory clinical data, quantitative analysis is required, as is the verification of herbal ingredients. Pharmaceutical companies, drug regulators, healthcare professionals, and patients all need to be aware of the possible dangers associated with these medications, as well as their role in reducing and managing those risks. Each application for authorization of a pharmaceutical product in the European Union must be prepared by the holders of Marketing Authorisations (MAH). Directive 2001/83/EC specifies the documents that must be submitted. Article 16c discusses the documentation requirements for traditional herbal medical products (THMP).[29] It is required to do a bibliographic evaluation of safety data (non-clinical overview), an expert report, and further data, if necessary. HMPC provides a framework for presenting the information and documents required for an application.[30]

In the present time, the large diversity of products available complicates polyherbal pharmacovigilance. Patients should be aware of their drugs and encouraged to notify their doctors, nurses, and pharmacists about them so that correct information on side effects, interactions, and efficacy may be provided. Data about polyherbal medicine should be available in a number of databases devoted to this field. Clinical trial procedures, on the other hand, do not cover all elements of medication safety. Non-clinical tests, such as long-term carcinogenicity and reproductive toxicity studies (teratogenic potential), are also required for a complete evaluation of safety. It's also important to understand the risks of hepatotoxicity, nephrotoxicity, neurotoxicity, and cardiotoxicity. The formulation of post-risk-management strategies for polyherbal medicine, with the help of regional toxicology and veterinary institutes, university pharmacognosy and botany departments, and botanical gardens, is crucial. Some critical improvements, such as a comprehensive set of *in-vitro* and *in-vivo* (rodent) genotoxicity testing, are required by non-clinical safety standards for any polyherbal medication. Strategies like spontaneous reporting and prescription event tracking should be used in the post-marketing monitoring of the polyherbal safety profile. To address botanical nomenclature, quality, adulteration, labeling concerns, prescriber/reporter differences, and under-reporting, these approaches must be modified.[31]

Regulatory Status of Herbal Medicines

Polyherbal medications have different legal statuses in different countries. Polyherbal knowledge is widespread in developing nations, and its usage in traditional medicine is widespread. However, there are no statutory conditions in place in these nations to incorporate these historically used polyherbal remedies under drug regulation. Most nations approve herbal medications based on traditional herbal references as long as they aren't recognized to be harmful when used to treat mild conditions. However, claims are being made these days that polyherbal remedies may treat more serious disorders for which there is no conventional understanding. Regulatory regulations for polyherbal medicines are therefore required to assure their safety, effectiveness, and quality, as well as to support particular purposes; scientific and clinical proof must be obtained. Different needs for clinical trial data and toxicity data vary depending on the type of herbs and market availability. The legal criteria for polyherbal medicines differ from one nation to the next. The general flow of PV is shown in Figure 4.

The construction of a three-tier network of national pharmacovigilance, intermediary pharmacovigilance centers, and peripheral pharmacovigilance centers is the goal of the central sector system of pharmacovigilance of Ayurveda, Siddha, Unani, and homeopathic medications. In the initial phase of implementation, the All-India Institute of Ayurveda in New Delhi has been designated as the national pharmacovigilance center, while five AYUSH

National Institutes have been designated as intermediary pharmacovigilance centers and 42 AYUSH institutions with clinical facilities have been designated as peripheral pharmacovigilance centers. It is hoped that more similar facilities will open around the country, bringing the total number of peripheral pharmacovigilance centers to 100. Representatives from the central drug standard control organization, which serves as the country's national drug regulatory body, and the Indian Pharmacopoeia Commission, which serves as the country's WHO collaborating center for pharmacovigilance, are mentors and guides for the initiative.

Future Prospects of Pharmacovigilance in Polyherbal

Adverse outcomes in polyherbal products and treatments are frequently caused by poor product quality or improper usage, as well as insufficient regulatory measures, quality control systems, and unregulated distribution methods. The WHO urges member nations to enhance national polyherbal medicine legislation, registration, quality assurance, and management in order to lower these occurrences. It also places a strong emphasis on consumer education and appropriate distribution practices. In addition, when it comes to the distribution of polyherbal medicines, national healthcare authorities ought to emphasize consumer education and qualified practice more.[32] The WHO has praised drug regulatory agencies and national pharmacovigilance centers for their active involvement in the formulation of these recommendations. This is a good place to start when it comes to enhancing agency-to-agency interactions, which is necessary to move the needle toward the common objective of polyherbal medicine safety.[33] The recommended technique is to include polyherbal medicines into existing national pharmacovigilance systems or, in the absence of such systems, to develop comprehensive national pharmacovigilance systems that encompass polyherbal medications. Consequently, the guidelines identify the special challenges that come with properly monitoring the safety of polyherbal drugs and offer options for overcoming them. There is also a method for reporting adverse reactions to polyherbal medicines.[34]

CONCLUSION

Controlled clinical studies and data are required to clarify and determine the importance of pharmacovigilance in polyherbal. Polyherbal medications are gaining popularity because of their ability to replicate or counteract the effects of pharmaceuticals. Data on the safety of these medications in various patient groups with different pharmacogenomics, metabolization profiles, and gut microbiota compositions are, however, lacking. Accurate data on the safety of polyherbal drugs must be gathered through effective pharmacovigilance in order to create sufficient guidelines for safe consumption.[35-37] The necessity for a thorough and critical assessment of the present status of polyherbal medicine pharmacovigilance initiatives at the national and international levels has arisen from the rise in the use of these medications around the world.[38] The goal of this study is to present a thorough assessment of the difficulties, new problems, and potential solutions for enhancing safety monitoring in polyherbal medicine.

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