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Review Article

Systematic Review of Global Practices and Challenges in Pre- and Post-Marketing Surveillance of Polyherbal Formulations

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Abstract

Background and aims: Polyherbal preparations have emerged as promising solutions for various diseases and conditions globally, owing to their combined benefits derived from multiple herbal plants. Despite their widespread utilization, significant gaps remain in the safety and efficacy of polyherbal products, particularly regarding the lack of pre-marketing and post-marketing surveillance.

Methods: The pre-marketing and post-marketing surveillance of polyherbal formulations were assessed through a review of literature from various sources, including books and databases such as PubMed, Google Scholar, and ScienceDirect, covering the period from 2007 to 2023. Only sources published in the English language were included in this review. A total of twenty randomly selected polyherbal preparations were subjected to a detailed examination for further identification, screening, eligibility assessment, and inclusion in the study.

Results: All selected polyherbal products available in the global market had undergone some form of pre-marketing surveillance, including in vivo, in vitro studies, or meta-analyses. However, post-marketing surveillance was found to be lacking for 85% of the selected polyherbal products. The limited data on long-term safety and efficacy, coupled with the absence of consistent follow-up, underscores a critical gap in ensuring product safety.

Conclusion: The increasing prevalence of polyherbal products in the market underscores the necessity for enhanced pre-clinical, clinical, and post-marketing studies. Improved regulation and monitoring are essential to ensure that these formulations are effective, safe, and associated with fewer side effects.

Keywords: Polyherbal preparations, Post-marketing, Pre-marketing, Product safety, Herbal-drug interaction

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Introduction

Polyherbal formulations consist of combinations of two or more herbs utilized in drug formulations within Ayurveda. Ayurvedic medicine adheres to two primary principles in formulation: the use of a single herb or the combination of multiple herbs, referred to as polyherbalism. This concept, which is unique to Ayurveda, has been well established and has achieved significant success in Western medicine, offering new hope to patients. The historical Ayurvedic text "Sarangdhar Samhita" emphasizes the notion of synergism in polyherbal formulations (1).

While single-herb formulations are recognized for their active constituents, these components are often present in small quantities, which may be insufficient to elicit the desired therapeutic effects. In contrast, polyherbal preparations have recently gained popularity worldwide due to several advantages not typically found in allopathic medicines. They demonstrate a broad therapeutic range (effective at low doses and safe at high doses), exhibit fewer side effects, are eco-friendly, cost-effective, and readily available. Consequently, nearly half of the population in many industrialized countries now regularly utilizes some form of traditional and complementary medicine, with usage rates reported as follows: United States, 42%; Australia, 48%; France, 49%; and Canada, 70% (2).

Synergism occurs when two or more compounds are combined to produce a total effect that exceeds the sum of their individual effects. This phenomenon is particularly

advantageous in polyherbalism, as it provides benefits that are often absent in single herbal formulations. The potential for achieving a higher therapeutic effect with a single multi-component formulation (3) means that a lower dosage of herbal preparations may be required to attain the desired pharmacological action, thereby reducing the risk of harmful side effects (4).

Moreover, polyherbal formulations simplify the treatment regimen for patients by combining multiple herbs into one product, eliminating the need to take several separate single herbal formulations simultaneously. This convenience can indirectly enhance patient compliance and overall therapeutic effectiveness (5). As a result of these combined benefits, polyherbal formulations have gained increased market popularity compared to single herbal formulations on a global scale.

Recent developments in Western medicine have been significantly influenced by the principles of traditional Ayurvedic medicine, as well as other traditional medical systems such as Unani, Kampo, and traditional Chinese medicine, all of which have thrived for thousands of years (6). This integration has been supported by modern scientific research and clinical trials, highlighting the relevance of these ancient practices in contemporary healthcare. The knowledge of plant-based remedies within traditional medicine has proven to be a vital resource in the discovery and development of modern pharmaceuticals (7). Many drugs currently in clinical use have origins in herbal plants, with numerous valuable medications traced back to their applications in traditional medicine (8). Consequently, the insights offered by traditional medicine are indispensable in advancing research and development efforts in modern drug discovery, which typically involves rigorous randomized controlled in vitro and in vivo clinical trials (9). Despite the widespread availability of numerous polyherbal preparations in the market, commonly used as alternative treatments for various diseases—often in conjunction with synthetic drugs—there has been a notable lack of scientific evaluations and post-marketing surveillance for these herbal products in the literature (10).

In the final stages of drug development, a drug undergoes testing on a group of volunteers or patients to secure the necessary approval for its market launch. Clinical trials consist of four phases, with the first three phases classified as pre-marketing trials and the final phase dedicated to post-marketing surveillance. Pre-marketing surveillance involves studies designed to assess both the safety and effectiveness of new compounds in human subjects (11). Post-marketing drug surveillance, on the other hand, entails the continuous monitoring of drugs after their release into the market for consumer use. This phase assesses drug usage across diverse situations and for extended durations (12). Pre-marketing surveillance is conducted in a clinical setting before a drug is introduced to the market, ensuring the safety and efficacy of newly developed drugs in humans. However, the number and types of patients involved in pre-marketing surveillance are generally limited compared to those who will ultimately be prescribed the drug (13). Therefore, further evaluation of drugs through post-marketing surveillance is essential for ongoing monitoring. This type of surveillance is particularly effective in identifying previously unnoticed positive or negative effects associated with a drug. The primary focus of post-marketing surveillance centers on monitoring and evaluating adverse drug reactions (ADRs). ADRs can occur due to the presence of multiple pharmacologically active compounds in polyherbal preparations and their potential interactions.

Moreover, the theoretical probability of herb-drug interactions is higher in polyherbal formulations compared to synthetic drug-drug interactions, as synthetic drugs typically consist of a single chemical entity (14). While polyherbal formulations provide numerous benefits to humanity, they also face certain unavoidable limitations that can affect their effectiveness and therapeutic potential, primarily due to a lack of extensive research. For instance, meadowsweet, a plant known for its anti-inflammatory properties, can displace highly protein-bound medications such as warfarin and carbamazepine. This displacement may lead to increased adverse effects associated with these drugs (10).

This review aims to evaluate the pre-marketing and post-marketing surveillance of polyherbal formulations currently available in the global market.

Materials and Methods

In this systematic review, the pre-marketing and post-marketing surveillance of currently available polyherbal formulations in the global market were assessed. A comprehensive literature search was conducted using various sources, including books from an Ayurvedic hospital in Pallekale, Kandy, Sri Lanka, as well as databases such as PubMed, Google Scholar, and ScienceDirect, covering the period from 2007 to 2024.

Relevant keywords, including "polyherbal formulation," "polyherbalism," "herbal medicines," "post-marketing surveillance," and "pre-marketing clinical trials," were employed to identify pertinent articles from the databases. The gathered research papers were subjected to a thorough examination process that included identification, screening, eligibility assessment, and inclusion criteria to ensure that only the most relevant and high-quality studies were considered for this review.

From the data collected, twenty polyherbal products available in the global market were randomly selected for this systematic review. To ensure an unbiased selection process, each product was assigned a random number using the Excel = RAND () function. The top 20 products from the sorted list were then chosen for inclusion in the review.

Each selected polyherbal product was subsequently evaluated for both pre-marketing and post-marketing surveillance. The flowchart below visualizes the selection

process of the sources for this systematic review, including the application of inclusion and exclusion criteria (Figure 1).

Furthermore, the proportion of products in each surveillance category was calculated as a percentage of the total selected polyherbal products. This data visualization was created using GraphPad Prism version 10.4.1 software, allowing for a clear representation of the distribution of products across the different surveillance categories.

Results

Pre-marketing surveillance

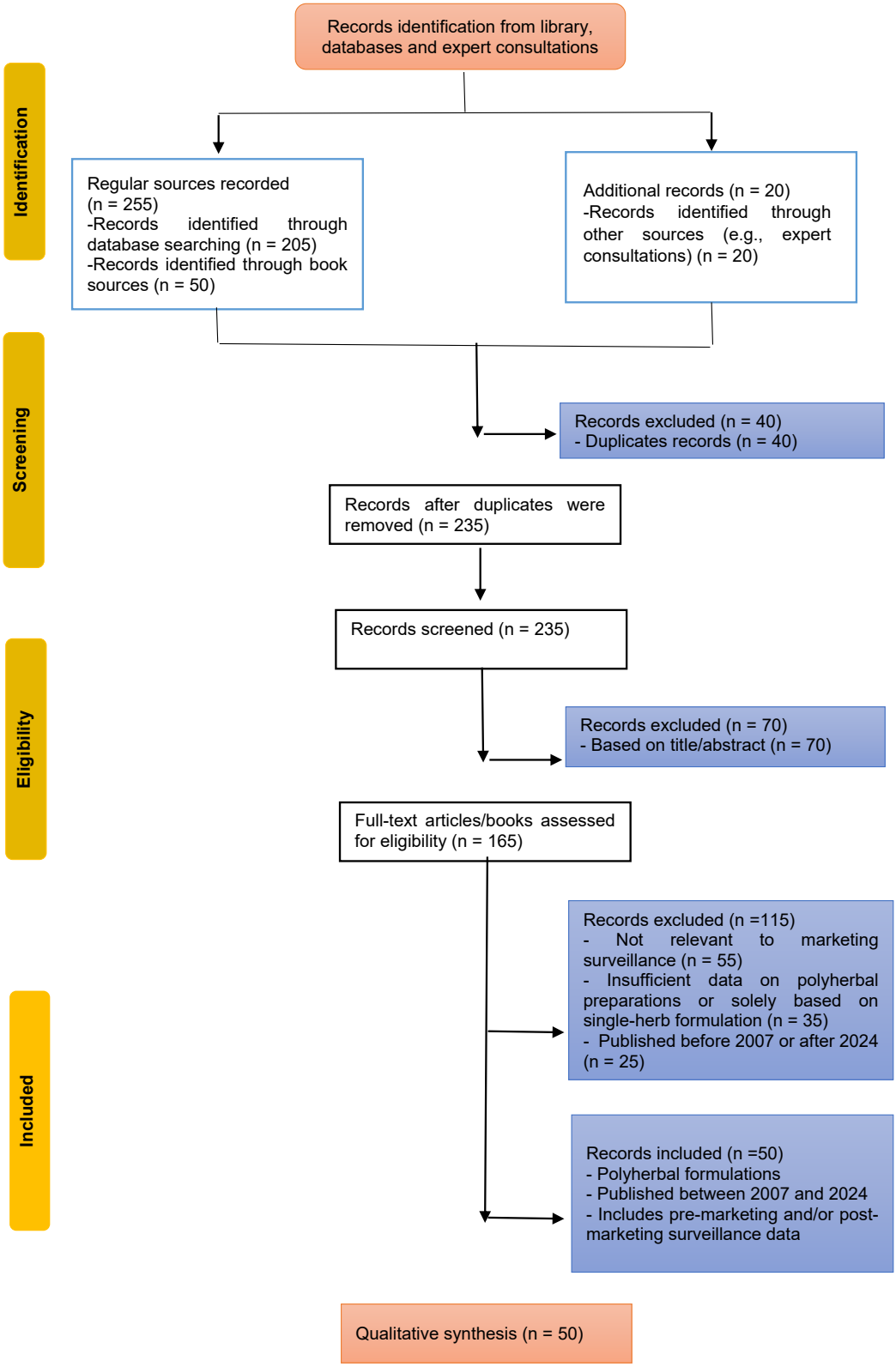

Figure 1. Flow chart for the selection process of data sources

In this systematic review, twenty polyherbal formulations obtained from various global markets were evaluated, with a focus on their pre-marketing and post-marketing surveillance data. The formulations exhibited significant variability in their composition and applications, encompassing a range of effects, including anti-inflammatory, anti-diabetic, antimicrobial, and anti-malarial properties (Table 1).

All products, including Wanderer Plus (China) and Praneem (India), underwent pre-marketing evaluations that encompassed in vivo pre-clinical trials and meta-analyses. Figure 2 illustrates the distribution of polyherbal formulations based on their marketing surveillance status, categorized into three groups: pre-marketing surveillance, post-marketing surveillance, and both types of marketing surveillance. The percentages represent the proportion of polyherbal products classified within each category. The data were derived from a systematic review of 20 polyherbal products available globally, covering the period from 2007 to 2024. Notably, only 15% of polyherbal products have undergone both pre-marketing and post-marketing surveillance (Figure 2). For instance, while Wanderer Plus was reported to cause dizziness and fatigue when used in conjunction with carbamazepine, many products, such as Diabrid (India) and Polyherbal Emulgel (India), had not been subjected to any post-marketing investigations. Ben-Cha-Lo-Ka-Wi-Chian (Thailand) and Habbe Gule Aakh (India) demonstrated promising results during pre-marketing evaluations; however, they lacked follow-up data regarding long-term safety and efficacy. Additionally, products like Zyflamend (USA) and Nefang (Cameroon) revealed adverse effects or specific safety concerns, including gastrointestinal damage and skin irritation, respectively. Overall, all selected polyherbal products in the global market had undergone some form of pre-marketing surveillance, such as in vivo studies, in vitro studies, or meta-analyses. Nevertheless, post-marketing surveillance was absent for 85% of the selected polyherbal products.

Discussion

The review indicates that post-marketing surveillance for

Table 1. Selected polyherbal formulations subjected to pre-marketing and post-marketing surveillance

Commercial name of the formulation and herbal ingredients included in the formulation	Country of origin	Dosage form	Pharmacological action	Side effects	Pre-marketing surveillance	Post-marketing surveillance
1. Wanderer plus, *Paeonia lactiflora, poria cocos fungus, Atractylodes macroephala, Paeonia suffruticosa, Gardenia jasminoides, Zingiber officinale, Glycyrrhiza uralensis, Bupleurum chinense, Anglica sinensis, Mentha haplocalyx*	China	Capsule	Depressive disorder (15)	None	*In-vivo pre-clinical trial* - Meta Analysis (16)	Dizziness and fatigue were reported in conjunction with the use of carbamazepine (17)
2. Praneem *Azadirachta indica* (Neem) along with purified Saponins from *Sapindus mukerosi* and Mentha citrata oil	India	Cream/ pessary	Contraceptive/ Vaginal microbicides	None	*In vivo* clinical trial phase II	Not investigated or no publicly available data are available (18)
3. Joshanda *Zizyphus jujuba, Onosma bracteatum* and *Glycyrrhiza glabra*	Pakistan	Unit-dose sachet	Anti-bacterial, common cold	None	*In-vitro*- Kirby-Bauer Disc Diffusion Method (19)	Metal ions were reportedly present in the formulation (20)
4. Ben-Cha-Lo-Ka-Wi-Chian Herbal ingredients -Unknown	Thailand	Powder	Anti-pyretic and antinociceptive	None	*In-vivo* pre-clinical trial using Rat Basophilic Leukemia cell line (21)	Not investigated or no publicly available data are available (22)
5. Diabrid *Gymnema sylvestre, Momordica charantia, Eugenia Jambolana, Trigonella graeceium*	India	Solution	Anti-diabetic	None	*In-vivo* clinical trial phase I (23)	Not investigated or no publicly available data
6. DHU001 *Ficus carica Linn, Liriope spicata Lour., Platycodon grandiorum Jacq., Schisandra chinensis Baill., Glycyrrhiza uralensis Fisch., Zingiber officinale Roscoe., Mentha arvensis* Linne var piperascens	South Korea	Solution	Contact dermatitis	Headache, nausea, dizziness	*In-vivo* pre -clinical trial - Mouse micronucleus test (24)	Not investigated or no publicly available data
7. Prasarani sandhan *Paederia foetida L., Piper longum L., Piper chaba Hunter. Plumbago zeylanica L., Zingiber officinale Roscoe., Allium sativum L*	Bangladesh	Powder	Immunomodulatory	None	*In-vivo* pre-clinical trial - Analgesic and anti-inflammatory models, carrageenan induced paw edema, acetic-acid writhing, and formalin induced paw lick tests in mice (25)	Not investigated or no publicly available data

Table 1. Continued.

Commercial name of the formulation and herbal ingredients included in the formulation	Country of origin	Dosage form	Pharmacological action	Side effects	Pre-marketing surveillance	Post-marketing surveillance
8. Polyherbal emulgel Tea tree oil, Lemongrass oil, Ginger oleoresin & Capsaicin and Cow Ghee	India	Emulgel	Anti-inflammatory	None	*In-vivo* pre-clinical trial - Complete Freund's Adjuvant (CFA) model in mice (26)	Not investigated or no publicly available data
9. Tongkat Ali *Eurycoma longifolia Jack.,Cistanche deserticola Y.C.Ma*	Malaysia	Capsule	Increase Sexual Stamina/ relieve stress	Insomnia, Irritability, Restlessness High doses damage gastrointestinal DNA	*In-vivo* clinical trial phase II (ongoing) (27)	Not investigated or no publicly available data
10. Normacid syrup *Ficus glomerata Roxb.* (Bark);, *Fagonia Arabica* L. (whole plant), *Vetiveria zizanioides Stapf* (root), *Santalum album* L. (wood) e.t.c.	India	Syrup	Anti – ulcer/ antioxidant (In treatment of peptic ulcers)	Headache, constipation, dizziness	*In-vivo pre-clinical trial*- Experimentally induced gastric ulcers in mice (28)	Not investigated or no publicly available data
11. Nefang *Mangifera indica, Psidium guajava, Carica papaya L, Cymbopogon citratus, Citrus sinensis, Ocimum gratissimum*	Cameroo	Solution	Anti-malarial	None	*In-vivo pre-clinical trial* - Plasmodium infected rodent models (29)	Not investigated or no publicly available data
12. Ovoutoline *Glycyrrhiza glabra, Saraca indica, Symplocos racemosa, Tinospora cordifolia, Asparagus racemosus, Valeriana walchii* and *Holarrhena antidysenteric*	India	Tablet	Post-menopausal symptoms	None	*In-vivo* pre-clinical trial – Toxicity test on mice (30)	Not investigated or no publicly available data
13. EMSA eritin Glycine max, *Cocos nucifera* and Red rice	Indonesia	Powder	Stimulation of erythropoiesis	None	*In-vivo* pre-clinical trial – Total Body Irradiation on mice	Progressing on cancer patients (31)
14. Daouri Khaya *senegalensis, Odina acida, Lophira lanceolata, Paullinia pinnata L.* and *Pteleopsis suberos*	Ghanna	Solution	Anti-diarrheal, anti- Malaria (for children)	None	*In-vivo* pre-clinical trial -Toxicity test on mice (32)	Not investigated or no publicly available data
15. Sharkaradhi Kalka, Chandra Kalka	Sri Lanka	Kalka (semisolid dosage form)	Antioxidant, anti-inflammatory activity	None	*In-vitro* - DPPH radical scavenging assay and *In-vitro* human red blood cell membrane stabilization assay (33)	Not investigated or no publicly available data
16. Derma heal cream Natural honey, Olive oil and Beeswax	India	Cream	Wound/ burn healing	None	*In-vivo* pre-clinical trial – Induced wound healing in mice (34)	Not investigated or no publicly available data
17. IBS herbal Chinese medicinal formula – 20 herbs	China	Unit-dose sachet	Anti-inflammatory	Gastrointestinal disorders (e.g., nausea, constipation, diarrhea, or bloating), Skin rashes	*In-vivo* pre-clinical trial - The Wrap Restrain Stress, The Water Avoidance Stress, The Maternal Separation and Chronic Stressors in mice (35)	Not investigated or no publicly available data
18. HabbeGuleAakh *Zingiber officinalis* (Rhizome), *Piper nigrum* (Fruit), *Calotropis gigantean* (flower), *Bans Bambusa* (leaf)	India	Powder	Anti-inflammatory/ analgesic	None	*In-vivo* pre-clinical trial - Wistar rats for anti-inflammatory activity while Swiss mice were used for analgesic activity)(36)	Not investigated or no publicly available data
19. Zyflamend *Ocimum sanctum, Curcuma longa, Zingiber officinale, Camellia sinensis, Rosmarinus officinalis, Polygonum cuspidatum, Berberisvulgaris, Origanum vulgar, Scutellariabaicalensis* and *Coptis chinensis*	The United States of America	capsule	Prostate cancer	Bad taste in the mouth, heartburn, and diarrhea, hypersensitivity (37)	*In-vivo* - cell cultures and in an orthotopic mouse model (38)	Not investigated or no publicly available data
20. Polyherbal carbopol- 940 gels *Plumbago zeylanica Linn, Datura stramonium* Linn and *Argemone mexicana* Linn	Malaysia	Topical gel	Antimicrobial, anti-inflammatory accelerated tissue remodeling (39)	Skin irritation (occasionally)	*In-vivo*–in mice skin permeation test using rabbits (40)	Not investigated or no publicly available data

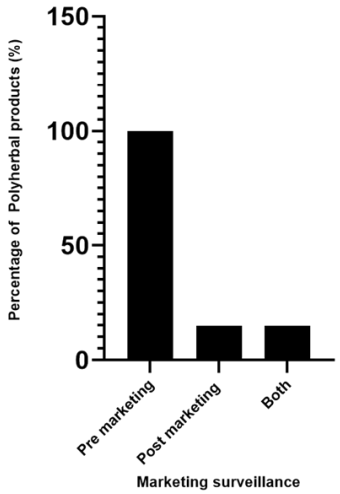

Figure 2. Distribution of polyherbal formulations by marketing surveillance status: A global analysis (2007-2024)

the evaluated polyherbal formulations is generally limited. Despite comprehensive pre-marketing evaluations, which include clinical trials and meta-analyses for many formulations, there is a notable absence of follow-up studies once these products are on the market. This gap raises concerns regarding the ongoing monitoring of product safety and efficacy after market entry. Strengthening post-marketing surveillance is crucial to ensuring the long-term safety of consumers and maintaining public confidence in polyherbal formulations. Furthermore, while side effects have been reported for several polyherbal products, the clinical significance, frequency, severity, and potential long-term impacts on consumers are not well elucidated or thoroughly investigated in the literature. Pharmacovigilance, defined as the science and activities related to the detection, assessment, prevention, and understanding of adverse drug effects, must be effectively adapted to include herbal products (41). While clinical trials and spontaneous reports remain the primary sources of data on adverse events, herbal medicines often circumvent rigorous post-marketing surveillance, as many are available directly as non-prescription products. In numerous countries, traditional and complementary medicine providers are excluded from adverse event reporting systems, underscoring the urgent need to expand national reporting schemes to collect safety data from all relevant practitioners and consumers.

Safety concerns arise from the lack of regulation governing herbal medicinal products, contributing to issues related to substandard quality and the inherent toxicity of certain products (42). Additionally, accurate recording and classification of herbal medicines are essential, with the WHO Drug Dictionary (WHO-DD) (43) and the Herbal Anatomical Therapeutic Chemical (HATC) classification (44) serving as key tools for ensuring standardized data entry. It is widely acknowledged that users of herbal medicines often refrain from disclosing their usage to healthcare professionals, and healthcare providers frequently neglect to inquire about their patients' use of these products (45). Even when information regarding herbal medicine usage is shared, healthcare professionals often lack sufficient knowledge about these products due to a dearth of research. Furthermore, in many instances, reliable information regarding the effectiveness of specific products or interactions between herbal and conventional medicines remains to be established (46).

Pharmacovigilance systems, originally designed for synthetic medicines, require adaptation to effectively monitor herbal medicines. The World Health Organization (WHO) emphasizes the importance of modifying these frameworks to ensure the safety of herbal medicines, addressing issues such as composition variability and potential contamination (47, 48).

Achieving clinical reproducibility with Ayurvedic polyherbal preparations presents notable challenges. While the Ayurvedic Pharmacopoeia of India provides guidelines for standardizing these preparations, reliance on this alone is insufficient to ensure consistency across batches. Factors such as the selection of raw materials—including their habitat, seasonal variations, harvesting methods, storage conditions, and processing techniques—play crucial roles in determining quality (49). However, the inherent variability in crude materials, influenced by geographical location, climate, environmental factors, and collection practices, complicates the maintenance of consistent quality in the final product. This batch-to-batch variability directly impacts the efficacy and safety of polyherbal preparations (50).

The establishment of adequate guidelines and a dedicated monitoring body could mitigate the occurrence of adverse incidents. For instance, Joshanda, a widely used polyherbal preparation in Pakistan, has been found to contain metal ions, raising concerns regarding toxicity associated with such formulations. The issue of metal ion toxicity remains unresolved within the context of polyherbal preparations (51). Experts in drug research have identified approximately 6,000 medicines listed in the "Ayurvedic Formulary" that intentionally incorporate at least one metal, with mercury and lead being the most frequently utilized. These toxic elements pose significant risks to patients, including nephrotoxicity, hepatotoxicity, neurotoxicity, and hematotoxicity. Conducting adequate clinical trials and post-marketing research is essential to effectively address these concerns (51).

Moreover, herbal-drug interactions are largely unidentified, with only a few documented examples. For instance, garlic (Allium sativum), ginger (Zingiber officinale), and ginkgo (Ginkgo biloba) have been reported to interfere with non-steroidal anti-inflammatory drugs (NSAIDs) and warfarin, potentially increasing the risk of bleeding (52). Additionally, the active components responsible for the purported therapeutic benefits are often unidentified or only partially understood. The situation is further complicated by the common Ayurvedic practice of using combinations of herbal ingredients to

create polyherbal formulations (53).

To ensure the safe use of polyherbal formulations, there is an urgent need for clear regulatory guidelines and the establishment of a dedicated monitoring body to oversee pre-marketing quality control. This oversight is particularly critical for detecting potential contamination with heavy metals, pesticides, and microorganisms. Comprehensive studies investigating ADRs associated with polyherbal products are essential, given the current data indicating a growing prevalence of such events. Enhanced surveillance and standardization of polyherbal products would not only minimize health risks but also improve patient outcomes, rendering this research highly relevant to healthcare professionals.

Furthermore, engaging key stakeholders—including traditional medicine practitioners, healthcare providers, and regulatory agencies—is vital to drive improvements in the quality and safety of polyherbal products. In addition, a thorough investigation into herbal-drug interactions is essential to support evidence-based patient care and ensure a comprehensive risk assessment of polyherbal products, akin to the approach applied to synthetic medicines.

To enhance the regulation of polyherbal products, it is crucial to establish clear guidelines for both pre-marketing and post-marketing surveillance. These guidelines should include mandatory clinical trials, safety monitoring, and long-term follow-up studies. Additionally, regulatory bodies should collaborate with manufacturers to ensure that all adverse effects are thoroughly documented, with transparency in reporting enforced. This can be achieved through the creation of standardized reporting systems and the incentivization of compliance via certification, similar to the frameworks established for synthetic medicines, but tailored specifically to the unique characteristics of polyherbal products.

The review has several limitations. The literature search of the study was limited to English-language publications and selected databases, which may have excluded important studies published in other language or indexed elsewhere. Further, random selection of twenty polyherbal products may not fully represent the diversity of global market. A more comprehensive approach, such as stratified sampling based on geographic region or product categories, could provide a better overview.

Conclusion

With the increasing number of polyherbal products, both pre-clinical and clinical trials, as well as post-marketing surveillance, remain limited. This highlights the critical need for rational drug management to ensure the optimal use of polyherbal formulations, focusing on achieving the highest quality, safety, and minimizing ADRs. Consequently, there is a significant need for enhanced study, follow-up, and regulation in both pre-marketing (including pre-clinical and clinical trials) and post-marketing surveillance. Such measures will help ensure that polyherbal formulations are not only more effective but also associated with fewer side effects, ultimately opening new possibilities in this field.

Authors' Contribution

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Competing Interests

The authors declare that they have no conflicts of interest to disclose.

Ethical Approval

Nil.

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