



REVIEW ARTICLE

Challenges in monitoring the safety of herbal medicines- an appraisal

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ARTICLE INFO ABSTRACT



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Introduction: Both the medical profession and the general public have started to place a lot of emphasis on drug safety and pharmacovigilance. The use of herbal remedies and phytonutrients is expanding quickly, with many people resorting to these items for the treatment of a range of health conditions in different national healthcare settings. Traditional herbal therapy is frequently used because it is less expensive; more closely aligns with the patient's beliefs, and fills a demand for more individualized healthcare. This promotes a more transparent public approach to health information. Around 80 % of the world's population depends on herbal remedies as their primary source of healthcare and traditional medicine.

Objective: This study aimed to investigate significant problems associated with monitoring the safety of herbal medicines and to assist the regulatory bodies in refocusing on the requirement for guaranteeing adequate public health protection and promoting safety.

Methods: The literature was obtained from online databases including Pub Med, Google Scholar, Web of Science, etc. A library search was also conducted from classical Textbooks, and published Books of herbal medicine. The keywords used for the search were pharmacovigilance, herbal medicine; adverse drug reaction; herb-drug interactions.

Results: Although numerous herbal medications are utilized and some of them have intriguing potential, very few of them have been evaluated, and their usage is not strictly regulated, so it is difficult to determine their potential adverse effects. This makes it challenging to determine the safest and most efficient therapies and to encourage the responsible use of herbal medicine.

Conclusion: Pharmacovigilance must be used to conduct an empirical clinical assessment to compensate for the lack of safety assessments of herbal drugs. This is only possible if herbal products are subjected to some sort of regulation so that adverse events can be traced.

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Introduction

Drug safety and pharmacovigilance have become a major focus for both the medical community and the public (Klepper & Cobert, 2010). Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem (WHO, 2004).

Complementary and alternative medicines (CAMs) refer to all non-biomedical remedies. WHO's traditional medicine strategy for the period between 2014 and 2023 is to focus on promoting the safe and effective use of herbal medicine and to utilize the potential contribution of CAM in healthcare (WHO, 2014; Zamawe et al., 2018).

The use of herbal medicines and phytonutrients or nutraceuticals continues to grow rapidly across the world, with many individuals now turning to these products for



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the treatment of a variety of health issues in various national healthcare settings (Ekor, 2014). According to estimates, up to four billion people (80 % of the world's population) who live in developing countries depend on herbal medicines as their main source of healthcare and traditional medical practice. They use herbs, as an essential component of the culture of their community (Bandaranayake, 2006; Bodeker, 2005; Ekor, 2014).

People are using herbal medicine to meet many healthcare needs, including disease prevention and to cure chronic illnesses such as dyslipidemia, hypertension, diabetes, cancer, and inflammatory bowel diseases (Awad & Al-Shaye, 2014; El-Dahiyat et al., 2020; James, 2018).

The most common reasons for using traditional herbal medicine are that it is inexpensive, more closely corresponds with the patient's beliefs, and satisfies a need for more personalized health care. This enables a more open public approach to health information (Benzie & Wachtel-Galor, 2011; El-Dahiyat et al., 2020).

As the global use of herbal medicinal products continues to expand rapidly and many more new products are introduced into the market, public health issues and concerns surrounding their safety are becoming more widely recognized. Although some herbal medicines have promising potential and are widely used, many of them remain untested and their use is also not monitored, therefore the knowledge of their potential adverse effects is very limited. This makes it difficult in identifying the safest and most effective treatments as well as the promotion of the rational use of herbal medicine (Ekor, 2014).

It is also well known that the safety of most herbal products is further jeopardized by a lack of effective quality controls, poor labeling, and a lack of pertinent patient information (Ekor, 2014; Raynor et al., 2011). Therefore, it has become imperative to provide the general public, including healthcare professionals, with sufficient information to promote a better understanding of the risks associated with the use of herbal products. The discussion in this review is related to the significant problems associated with monitoring the safety of herbal medicines and assisting the regulatory bodies in refocusing on the requirement for guaranteeing adequate public health protection and promoting safety.

Challenges related to the regulation of herbal medicines

Comprehending the use and safety of herbal drugs is challenging largely owing to the lack of regulation and the paucity of data on their utilization, effectiveness, and safety. The safety data of herbal drugs are largely derived from anecdotal case reports as the reporting of adverse drug reactions is sparse (Lam et al., 2005). National regulation and registration of herbal medicines vary from one country to another. Herbal medicines can be

categorized as either prescription or non-prescription medicines in jurisdictions where they are regulated (WHO, 2004). A single medicinal plant may be classified as a food, a functional food, a dietary supplement, or a herbal medication in different countries depending on the rules that apply to foods and medicines. Due to this, it becomes extremely difficult to define the concept of herbal medicines for national drug regulation, and it also confuses patients and customers (WHO, 2005). Additionally, herbal products that are classified other than as medicines and foods are growing in popularity, and there is a risk of adverse reactions because of lack of regulation, inadequate quality control measures, and sloppy distribution networks (including mail order and Internet sales) (Ekor, 2014). National regulatory information on herbal medicines is often not shared between national regulatory authorities and national safety monitoring and/ or pharmacovigilance centers (WHO, 2004).

Challenges related to the quality assurance of herbal medicines

Every country that regulates herbal medicines should have quality assurance and control measures, such as national quality specifications and standards for herbal materials, good manufacturing practices (GMP) for herbal medicines, labeling, and licensing schemes for manufacturing, imports, and marketing. These measures are vital for ensuring the safety and efficacy of herbal medicines (Ekor, 2014; WHO, 2004). Many botanical supplements are potentially unsafe because of adulteration and misbranding. Many of these adulterants are not detected until patient illnesses are first detected (Dreskin, 2000). There are other risks of contamination to botanical supplements. Products may differ substantially in their active content due to pressure on the supply of cultivars for botanical supplements. There is pressure to generate a product in the era of limited resources, with growing utilization and diminishing wild output. Raw material costs may override the quality and purity of the product. There are few barriers to bringing new products to the market and many newer entrants may lack the expertise to prevent quality issues and contamination in their products (Lam et al., 2005). This creates the potential for inadvertent poisoning as a result of overdosing or contamination as well as treatment failure through underdosing. Indeed, a study of botanical consistency found that only 43% of the products tested were consistent with either ingredients and dose with the benchmark or recommended daily dose. Twenty percent had the correct ingredient but not the stated dose and 37% were not consistent with either ingredient; the dose or the labeling was too vague to conclude (Garrard et al., 2003; Lam et al., 2005).

Challenges related to the complexity of herbal medicine

Herbal medicines are chemically complex mixtures containing multiple major and minor constituents with multiple potential targets and mechanisms (Normile, 2003). Research protocols, standards, and methods needed to evaluate the safety and efficacy of herbal medicines are very complex when compared to conventional pharmaceuticals (WHO, 2005; Zhou et al., 2013). There may be hundreds of natural elements in a single herbal medicine or medicinal plant, and a mixed herbal medicinal product may contain several times that number (WHO, 2005). In comparison to other pharmaceuticals, finished herbal products particularly for a mixture of herbal products, have much more complicated requirements and methods for quality control. The quality of such products is affected by the caliber of the raw materials used. Therefore, it is crucial to take appropriate measures such as good agricultural and good collection practices (GACP) for medicinal plants, including plant cultivation and selection (WHO, 2003).

Challenges related to lack of proper knowledge of herbal medicines

Healthcare professionals, such as doctors, nurses, and pharmacists, may lack knowledge or have little training on how herbal remedies affect their patients' health as many of them take other medicines, prescription or non-prescription. Appropriate knowledge is very important for diagnosis and treatment decision-making. Globally, the use of medicinal plants is the most common form of traditional medication. Herbal medicines are used within many different healing traditions with diverse knowledge bases and so there is still a question as to their suitability. Traditional medicines are increasingly being used outside the confines of traditional cultures and far beyond traditional geographical areas without adequate knowledge of their use and the underlying principles (WHO, 2004).

The majority of botanical drug products are used without medical supervision. Only 8% of those who use herbal drugs do so under medical supervision and 85% of those who treat themselves with herbs do not seek professional guidance or advice (Lam et al., 2005). Additionally, they are also being used in different doses, extracted in different ways, and used for non-traditional indications (WHO, 2004). Furthermore, most manufacturers of herbal medicines lack knowledge or place little emphasis on the importance of taxonomic botany and documentation, which creates unusual obstacles during the identification and collection of medicinal plants used for herbal remedies (Farah et al., 2000). Adopting the most commonly used binomial names for medicinal plants (including their binomial synonyms) is required to remove confusion caused by common names. For example, there are at least eleven different common names for *Artemisia absinthium* L., which contains an active narcotic

derivative and is capable of causing CNS disorders and generalized mental deterioration. Seven of the common names are completely different from their botanical names. Due to the widespread use of common names, *Heliotropium europaeum* (heliotrope), which contains potent hepatotoxic pyrrolidine alkaloids, is often mistaken for *Valerian officinalis* (garden heliotrope), which is known to contain valepotriates with sedative and muscle relaxing properties. This explains why it's crucial to include the exact scientific name of the plant, the plant part used, and the name of the manufacturer when reporting adverse drug reactions of herbal medicines. Therefore, for monitoring the safety of herbal medicine there must be an effective collaboration between botanists, phytochemists, pharmacologists, and other major stakeholders (Ekor, 2014).

Challenges related to consumer/providers' attitudes to herbal medicines

The idea that "natural" equates to "safe" is a common fallacy, and many consumers believe that natural therapies carry no risk. Patients using herbal medicines and other medicines together, frequently fail to inform their doctor that they are taking herbal medications as well (WHO, 2004). It has been estimated that up to 60% of patients who use alternative medicines never informed their physician (Foster, 2000; Halsted, 2003; Navo et al., 2004).

Furthermore, only 40% of doctors inquire about alternative medicine with their patients. There is undoubtedly a communication gap between patients and physicians. Some patients may fear disapproval by physicians and want to provide socially acceptable answers (Eisenberg, 2001).

Many people might truly believe they are ingesting a medication that has undergone extensive testing and is regulated. Although the vast majority of products are generally safe, many likely have low-level undocumented adverse effects. There is still a chance that many harmful occurrences will go unnoticed and untreated. This raises the risk that many adverse events likely go unnoticed and untreated. Healthcare professionals and providers of herbal medicines should ask patients directly, respectfully, and persistently what other medicines patients are taking, including prescription medicines or non-prescription medicine (Lam, 2005).

Challenges related to herb-drug interactions

Herb-drug interactions (HDI) have been a significant cause of adverse drug reactions (Lam, 2005). A drug interaction is defined as the modification of the effect (therapeutic effect and/or toxicity) of a drug by the concomitant or previous administration of another drug or food (Ruiz, 2010). One of the most significant clinical concerns with the concomitant consumption of herbs and prescription drugs is HDI. The requirement of polypharmacy in the treatment of the majority of disorders

further raises the risk of HDI in patients. The ability of intestinal and hepatic CYP to metabolize a variety of structurally unrelated compounds, apart from being responsible for the poor oral bioavailability of numerous drugs, accounts for the high number of documented drug-drug and drug-food interactions (Quintieri, 2008). This is more so, considering that oral drug delivery is mostly employed in the management of disease conditions in which, drug interaction alters both the bioavailability and pharmacokinetic disposition of the drug. This alteration and the resulting poor control of plasma drug concentrations would particularly be of concern for drugs that have a narrow therapeutic window or a precipitous dose-effect profile (Aungst, 2000; Perucca, 2006).

Pharmacotoxicity and treatment failure are two of the two main extreme challenges posed by the potential of a pharmacokinetic drug interaction. The former may be caused by the inhibition of the metabolic enzymes responsible for the metabolism and clearance of the drugs while the latter may be the result of enzymatic induction leading to faster drug metabolism. This is in addition to the intrinsic pharmacodynamic actions of the herbal products themselves which may include potentiating, additive, antagonism, or neutralization effects. HDI was frequently overlooked by physicians until recently for several reasons. Most trained physicians are not knowledgeable enough about herbal medicines and their potential for drug interactions (Clement et al., 2005; Fakeye, 2008; Ozcikir., 2007).

While the potential for interaction can be understood, it is much harder to describe the effect quantitatively or recommend dose modifications or usage. Herbal drugs have multiple unknown components that are not well defined and vary from product to product and are used at very different doses and in a very variable time with drug use. Current labeling recommendations, therefore, urge avoidance of a co-administration of drugs that interacts with it in a clinically significant way, rather than adjustment of the drug dose or dosing interval, a recommendation that is common for dealing with drug-drug interactions (Lam, 2005).

Challenges related to self-medication practices

Treatment of self-recognized diseases or symptoms by the patient with the use of medicinal products is known as self-medication. The patient's active participation in his or her health care may be one advantage of self-medication. However, there are potential risks associated with self-medication, such as incorrect self-diagnosis, delays in seeking medical advice when needed, severe adverse reactions, dangerous drug interactions, masking of severe disease, risk of addiction, and abuse (WHO, 2000).

Herbs are categorized as dietary supplements rather than pharmaceuticals; thus, producers are not required to show evidence of their product's efficacy or safety before

putting them on the market. Herbal remedies may be misused as a result of the widespread belief in the community that they are safe. In both industrialized and developing nations, improper consumption can result in toxicities and unintended side effects (Yusuff & Tayo, 2011).

Self-medication is theoretically open to the general public. However, there is a substantial risk of intoxication for some herb users (Huxtable, 1990). It has been demonstrated that self-medication is highly prevalent in the general population around the world. In a systematic review involving 70 studies on self-medication practices, the reported prevalence of self-medication was higher than 50% in 53.8% of the studies. Additionally, it was shown that developing countries have higher rates of self-medication (Shaghghi et al., 2014). The prevalence rates are consistently rising, especially among young people, which can be ascribed to socioeconomic factors, lifestyle, greater availability of medicinal products, easy access to health information, etc. (Galato et al., 2009). Responsible self-medication involves the use of approved medicines, available without prescriptions (OTC drugs), and are generally regarded as safe and effective when used as directed (Shehnaz et al., 2014).

The term "responsible self-medication" has been coined to highlight potential individual and social benefits associated with self-medication practices, such as increased access to efficient treatment and less strain on the healthcare system as a result of fewer visits to physicians (Noone & Blanchette., 2018). On the other hand, irresponsible or irrational self-medication, typically with prescription-only medications, increases the chances of direct harm to the patient in the form of adverse drug reactions (Albusalih., 2017). However, even when used responsibly, Self-medication is associated with several dangers and risks for the community such as a delay in diagnosis and incorrect diagnosis, the occurrence of drug-induced diseases, and the growth of public health expenditure (Tomas Petrović et al., 2022).

Conclusion

Any fault in the herbal medicine-practitioner-patient triangle compromises the safety of the medicine. Pharmacovigilance must be used to conduct an empirical clinical assessment to compensate for the lack of safety assessments of herbal drugs. This is only possible if herbal products are subjected to some sort of regulation so that adverse events can be traced. To make sure that practitioners and other healthcare personnel are capable of giving patients safe and appropriate advice, continuing professional awareness programs are required.

To rationalize herbal formulations and improve safety, it is vital to use systems-based approaches for the complex chemical interactions occurring in herbal combinations.

In the present scenario, global research on the safety of herbal medicine is still not up to the mark. There is a need to focus on the toxicity of common herbal medicine. Herb-drug interaction is a major challenge to the safety of herbal medicine, it should be focused on in research.

Active pharmacovigilance or the spontaneous reporting system is useful for detecting therapeutically pertinent safety concerns in clinical safety monitoring. A regulatory framework for herbal medications can provide customers with more assurance. However, the specification and regulation of herbal medicines varied greatly between countries.

Herbal remedies are treated as dietary supplements, functional foods, health products, or pharmaceuticals, leading to inconsistent standards and an unorganized market. The World Health Organization should suggest global unified planning to ensure the quality and safety of herbal medicines, which includes global management standards and quality standards, radical source of herbs, seed and seedling breeding, planting, harvesting, and storage, rational proceeding, manufacture, and quality standards.

Safety guarantee systems play an important role in maintaining human health. Therefore, rational clinical practice and risk monitoring should be established to improve the safety of herbal medicine.

Conflict of interest

The authors declare no conflict of interest concerning the research, authorship, and /or publication of this article.

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Authorship Contribution statement

Muzafar D A and Rabia M did Collection of the data. Muzafar D A B drafted and edited the manuscript. All the authors read and approved the final version of this manuscript.

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