

Pharmacovigilance of herbal and traditional herbal medicines

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Introduction

The use of herbal, traditional herbal medicines and phytonutrients continues to spread rapidly on global level and many people are resorting to the use of these products to treat various health conditions. The past decades have witnessed a huge wave of acceptance and public interest in natural therapies in both developing and developed countries, and this is due to the fact that herbal and traditional herbal medicines are available not only in pharmacies, but also in health food stores and supermarkets. It is estimated that up to four billion people (representing 80% of the world's population) living in developing countries rely on herbal medicine as their primary source of health care, and traditional medical practice involving the use of herbs is considered an integral part of their culture. Studies have shown that 14% - 31% of patients who take prescription drugs, take herbal medicines as a dietary supplement as well (Ekor, 2014).

Different traditional medical practices have been developed in different cultures and regions, without appropriate development of international standards and safety assessment methods for their control. Countries face major challenges in developing and enforcing traditional, complementary / alternative and herbal medicines. These challenges are related to regulatory status, safety and efficacy assessment, quality control, safety monitoring and lack of scientific knowledge for this type of products

within national drug regulatory bodies (Mukherjee, 2019).

Unlike conventional medicines, herbal medicines are chemically rich compound that can contain several hundred constituents. For many herbal medicines, their constituents are unknown, and even in those with well-documented phytochemistry, the ingredients responsible for pharmacological activity may not be precisely defined. Therefore, the chemical complexity of herbal medicines makes it difficult to determine their clinical pharmacokinetics, pharmacodynamics and toxicology, so in cases where safety concerns have been identified while taking an herbal medicine, there are difficulties in determining which constituent or combination caused the problem (Barnes, 2003).

Many herbal derived drug-preparations on the market do not have detailed pharmacology and toxicology, so pharmacovigilance is essential in detecting their side effects. In addition, there is a persistent problem of unexpected toxicity of herbal medicines due to problems with their quality (poor quality herbal material, incorrect or misidentified plants, and incorrect processing methods, as well as use of counterfeit or contaminated plants or products). These quality problems can be overcome to some extent with improved regulation requiring GMP production standards. However, herbal remedies come from many countries with different production standards and regulations, so poor-quality products are likely to remain a problem.

Materials and methods

Relevant European, American and Macedonian legislation has been revised, in particular Directive 2010/84/EU, Regulation (EU) 1235/2010, other regulations, as well as PubMed, Medline and supplementary relevant empirical analysis article websites, assessing the impact of European and non-European regulatory activities.

Results and discussion

The safety of herbal medicines is a serious problem for regulatory bodies, and in this regard, in 2005, the WHO published a report on national policies for traditional medicine and herbal medicine regulation, based on the first global study on traditional and complementary medicine. WHO conducted a second global survey during 2010-2012 and a follow-up survey during 2016-2018 (updated survey). In 2019, the WHO issued the Global Report on Traditional and Complementary Medicine, as part of the WHO Strategy for Traditional Medicine 2014-2023. In accordance with the two WHO Strategies for Traditional Medicine 2002-2005 and 2014-2023, and relevant World Health Assembly resolutions, Member States are taking steps to promote the safety, quality and efficacy of traditional and complementary medicine.

In 2013, the Global Coalition for Regulatory Science Research (GCRSR) was formed under the leadership of the US Food and Drug Administration (FDA). This coalition is joint body from 10 countries, including the European Union (EU), which aims to improve regulatory scientific research on the safety and efficacy of food and medicine. To achieve these goals, annual GSRS conferences have been established (so far 10 conference were held) and the topic of the last GSRS21 conference was "Food / Drug Safety Regulatory Sciences with real-world data and artificial intelligence".

To better address quality issues, pharmacopoeias around the world (United States Pharmacopoeia, the European Pharmacopoeia, and the Pharmacopoeia of the People's Republic of China) are setting quality standards for a growing number of herbal medicines and dietary supplements.

The main challenges related to safety monitoring of herbal and traditional herbal medicines are the non-compliance of the regulatory framework worldwide and the insufficient education of healthcare professionals for the side effects and toxic effects related to their use, the possibility of induction / inhibition of CYP enzymes, as well as interaction with conventional medicines. The primary challenge to start any discussion related to the regulation in this area is the lack of a global consensus on

product definition and categorization. Depending on the regulations, a medicinal plant can be categorized as food, functional food, dietary supplement or herbal medicine. This introduces serious difficulties in defining the concept of herbal medicines for the purposes of national drug regulation, and at the same time confuses patients and consumers. An additional problem in R. N. Macedonia are the "borderline products", a category that does not exist in any country worldwide, and usually includes products that are classified as dietary supplements in other countries.

To overcome the challenges associated with the safe use of herbal and traditional herbal remedies requires proper education of health professionals, especially the pharmacist, encouragement of the patients and healthcare professionals to report adverse events and continuous improvement of the pharmacovigilance system.

Conclusion

Collaborative approach among global regulatory agencies is inevitable in order to improve and harmonize the regulatory framework for guiding the safe utilization of herbal and traditional herbal medicines. Most of the herbal and traditional herbal medicines are available without prescriptions at the community pharmacies and could be obtained even in the supermarkets. Lack of awareness and knowledge for the potential of these medicines to cause toxic or side effects as well as interactions with conventional drugs is identified for both, consumers and healthcare professionals. In this direction, pharmacists play pivotal role in patents consulting when dispensing of herbal medicines, as well as in identification of potential risks for interactions, toxicity and reporting of adverse events in national pharmacovigilance systems. Well established pharmacovigilance system, appropriate education, communication skills and high level of awareness among healthcare professional for potential hazards of herbal medicines is important in order to maintain a positive benefit-risk ratio of herbal drugs and safety of public health.

References

- Barnes, J., 2003. Pharmacovigilance of herbal medicines: a UK perspective. *Drug Saf.* 26(12), 829-851. doi: <https://doi.org/10.2165/00002018-200326120-00001>.
- Ekor, M., 2014. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front. Pharmacol.* 10(4), 177. doi: <https://doi.org/10.3389/fphar.2013.00177>
- Mukherjee, P., 2019. Quality Control and Evaluation of Herbal Drugs (edition missing). Elsevier Science. Retrieved from <https://www.perlego.com/book/1828286/quality-control-and-evaluation-of-herbal-drugs-pdf> (Original work published 2019)