Herbal pharmacovigilance in Nepal: challenges and recommendations [version 1; peer review: awaiting peer review]

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Abstract
Traditional herbal medicine is widely used globally. Despite its extensive use, there are no proper regulations on standardization and use of herbal medicinal products. Nepal has a rich biodiversity and demography comprising of different socio-ethnic groups. Herbal medicines are utilized prominently in Nepalese communities. These herbal products may cause side effects and adverse effects, such as nephrotoxicity, neurotoxicity with the heavy metal toxicity associated with their powdered dosage forms. The side effects of using herbal products have been documented, such as bleeding with use of Ginkgo biloba and increase in blood pressure with use of Ephedra. Regulation of herbal products is essential to promote their optimal and rational use. Standard tools are available for assessing adverse effects of herbal products from health authorities, like the World Health Organization. In Nepal, self-medication practice using traditional herbal medicines is common and includes the concomitant use of allopathic. There is no focal point to address the regulatory issues on herbal products currently in Nepal. The Department of Drug Administration in Nepal is nominated as a national pharmacovigilance center and there are no reports on adverse events from the use of herbal medicines so far. However, not having any reports does not ensure the absolute safety and effectiveness of herbal products, so vigilance is warranted. Herbal pharmacovigilance is needed for Nepal to ensure safe and effective use of herbal medicines as the current pharmacovigilance ecosystem does not capture those cases. In the Nepalese context, the absence of reporting mechanisms may have underreported adverse cases of herbal products. The present opinion article aims to discuss the use of herbal products in Nepal, the challenges associated with the adverse reaction due to herbal medicines, and recommendations to overcome these challenges

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**Introduction**

Based on indigenous knowledge, the traditional practice of herbal medicines is widely prevalent in the world for preventive and therapeutic purposes to maintain good health and wellness of an individual. The use of traditional medicines from natural sources is a common phenomenon in South Asia, and uses of traditional medicine, mostly of plant origin, have been widely reported among south Asian countries. The Indian system of medicine, such as the Siddha and Ayurveda, relies heavily on the products derived from plants. Likewise, individuals in Pakistan have been using alternative therapies that are practiced by healers, clergymen, hakims, homeopaths and even quacks.

However, none of these South Asian countries, such as Nepal, India and Pakistan, has a proper system for herbal pharmacovigilance, nor is there proper regulation and research to regulate and standardize the production and use of herbal medicinal products. Lack of stringent regulation and reporting mechanisms may have missed many reports of toxicity in the country. This article aims to discuss the use of herbal products in Nepal, the challenges associated with the adverse reaction due to herbal medicines, and recommendations to overcome these challenges.

**Herbal product use in Nepal**

Nepal is a biodiversity-rich country because of its variation in the natural topography. Herbal medicines are widely used in Nepal, sometimes as an alternative to allopathic medicines or concomitantly with allopathic medicines. There is a general belief that traditional medicines are safe, effective and less costly compared to allopathic medicines. Nepal is also rich in culture and tradition where different ethnic groups celebrate different festivals and different medicinal plants are used on those occasions. For instance, in one of the biggest festivals, Dashain (celebrated in September-October), devotees use yellowish plant shoots called Jamara in Nepalese vernacular language (germinated from the seedlings of maize, barley, wheat, etc.). Wheatgrass (Triticum aestivum linum) juice is used in Nepalese society as it contains a number of vitamins, minerals, amino acids, and vital enzymes, which play an important anticancer role. Recently senior hepatologist in Nepal have claimed that there are severe side effects of drinking wheatgrass juice in patients. Herbal cough syrup containing ginger, Adhatoda vasica, Glycyrrhiza glabra and Ocimum sanctum, are also commonly used in Nepal. A phase IV comparative randomized trial from Pakistan showed that cough syrup containing Adhatoda vasica has a favourable impact on cough and associated symptoms in children.

In Nepal and elsewhere, the use of wild plants for producing herbal medicines is quite common, especially among traditional communities and tribal people. Nepal is one major supplier of wild medicinal plants in the world. Nepalese wild plants, such as Swertia chirata, Astarile rivularis, Bergenia ciliata, Acorus calamus, Nardostachys grandiflora and Valeriana jatamansi are used by local people, traditional healers and herbal medicinal companies to prepare different types of herbal medicines.

More studies are needed to know about side effects of these herbal drug products.

**Herbal pharmacovigilance globally**

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problem. No medicine is free from side effects, be it allopathic or ayurvedic. Therefore, it is clear that besides therapeutic effects there may be systemic and/or topical side effects of herbal medicines in various body systems. This is of great concern for health regulatory authorities, like the World Health Organization (WHO), to ensure the safe and effective use of traditional herbal medicines, which covers herbs, herbal materials, herbal preparations, and finished herbal products.

In developed nations, the use of herbal medicines as a dietary supplement is gaining momentum in the nutraceuticals market, making standardization, quality control and clinical trials of herbal medicines mandatory. However, even for the USA and European countries, setting up and maintaining a pharmacovigilance system has been a challenge because current pharmacovigilance systems are mostly focused on allopathic medicines, and herbal medicines come from countries of different origins than the country in which they are used, e.g. the USA and Europe. Nevertheless, various tools exist to aid individuals to carry out herbal pharmacovigilance. For example, RUCMAS (Roussel Uclaf Causality Assessment Method) is a standard tool that has been widely used in many countries for assessing drug-induced and herb-induced liver injury.

The distinction in the regulation of herbal medicines in developed and developing nations have sensitized the WHO to include traditional herbal medicines in pharmacovigilance programs for their safe and effective use, and quality control.

**Challenges to herbal pharmacovigilance in Nepal**

In Nepal, the Department of Drug Administration (DDA) has been nominated as the national pharmacovigilance center by the Uppsala Monitoring Center (UMC), Sweden, for reporting of adverse drug reactions. Herbal (Ayurvedic) medicines in the market possess variation in quality control due to a lack of quality standards and stringent regulatory environment. The DDA raised the issue of significant heavy metal content in herbal products being marketed by street vendors in its bulletin ‘Drug Bulletin of Nepal’; however, regulation and monitoring aspects are at a very early stage. Self-medication of traditional herbal medicines is also very common among Nepalese individuals, and additionally, it is unknown if the concomitant use of both herbal and allopathic drugs may interact resulting in adverse drug events. The public also have a general belief that these herbal medicines are safe.

Though the DDA acts as a national pharmacovigilance center, there are no reports of adverse events so far due to traditional herbal medicines in Nepal. The Department of Ayurveda (DoAy) under the Ayurveda Health Policy, 1996, was developed...
to regulate herbal medicines in Nepal. The central Ayurvedic hospital established at Nardevi, Kathmandu in 1933, and Midwestern Regional Ayurvedic hospital established in Dang contributed to the promotion of the use of Ayurvedic herbal medicines. There are more than 216 zonal Ayurvedic dispensaries throughout the country. Herbs Production and Processing Company Ltd. was also established at Jadibudi, Kathmandu to produce herbal products. National Ayurveda Formulary has been published by DoAy25. Yet, there is no such effective implementation of policy, investigations and quality control of herbal products36,26. Stringent implementation of the policy is yet to be seen in the country.

There is a necessity for herbal pharmacovigilance in Nepal. However, several challenges exist for the development of herbal pharmacovigilance system in Nepal. Standardization of herbal products with respect to active ingredients is a tedious process that are yet to be performed in Nepal30. Reporting of adverse events of herbal medicines is not mandatory in Nepal27,28. The challenge remains the same for drugs other than Ayurvedic drugs. Underreporting of adverse drug reactions is common in Nepal as well. There are many factors that can affect the reporting of adverse drug reactions like lack of knowledge and perception among healthcare professionals, shown by a systematic review29. A study done in Nepal also suggests that there are reasons like availability of less time for these activities. Also, a lack of confidence to certify the occurrence of any adverse drug reactions has been listed as a reason for underreporting30,31.

There is an adulteration of heavy metals in herbal medicines and chances of microbial contamination, which may deteriorate the quality of herbal products32. Most herbal medicines are provided by traditional herbal practitioners in different regions of the nation, which makes it difficult to assesses severe effects of easily accessible herbal medicines in every corner of the nation. In addition, there may be problems in the identification of medicinal plants, since all the medicinal herbs present in Nepal are yet to be explored.

The study done by Poudel et al. has proposed that there is an enormous requirement for the advancement of regulations for the screening of herbal fixed dose combinations (FDCs) to ensure their safety, efficacy and optimum utilization19. Regardless of the uncertain health advantages of the herbal FDC products, these have become common practice in developing countries34.

**Recommendations to overcome challenges**

To overcoming existing challenges in Nepal, we suggest the following recommendations for herbal pharmacovigilance:

i. Healthcare professionals should be actively engaged in reporting adverse reactions caused by herbal medicines. Pharmacists should ask patients about herbal medicines when obtaining medication history. Physicians should be aware of patients taking any herbal products as dietary supplements or for any other purpose before prescribing any drugs and should counsel on the interaction and adverse effects of these, if any43.

ii. Pharmacists should communicate properly with the patient and the physician before dispensing medicines, including herbal ones. Patients should also be asked for their past drug history and any allergies using any medicine.

iii. Patients should be encouraged to inform their physicians or pharmacists about herbal medicines they were or are taking.

iv. Hospitals, both government or non-government, including Ayurvedic hospitals, should contain herbal pharmacovigilance centers. These pharmacovigilance centers should focus on reporting any possible adverse effects caused by herbal products. Healthcare professionals working in the pharmacovigilance center should be aware of drug interactions between herbal medicines and the disease of the patient.

v. Education programs targeting all stakeholders, such as Ayurvedic physicians, pharmacists, target users and policymakers, should be should emphasize the use of herbal products, their therapeutic uses, side effects, interactions with conventional drugs, and any potentially fatal cases listed and this should be conducted regularly as a part of continuous medical education sessions for the prescribers.

vi. Good Manufacturing Practice guidelines should be strictly implemented for herbal medicine formulation, along with a test of batch safety, inspections, and other quality regulation36.

vii. National drug authorities, such as the DDA, DoAy, Nepal Ayurveda Medical Council and Nepal Health Research Council, must focus on ensuring quality control of marketed herbal products.

viii. A National Pharmacovigilance Center should also emphasize the effects of traditional medicines and establish a causality relationship for the prediction of probable adverse effects due to herbal products. Social media may also play a vital role in the signal generation of suspected adverse reactions due to herbal medicines like an allopathic medications37.

ix. As many patients use herbal medicines as self-medication along with allopathic medications, the prescribers or pharmacists must check for drug interactions with herbal products.

The proposed implementation of herbal pharmacovigilance centers can be conducted in a similar way to already existing pharmacovigilance centers that deal with allopathic medicines. Their implementation can be conducted via the DDA in collaboration with regional Ayurvedic centers, such as Naradevi Ayurvedic Hospital, Tribhuvan University Ayurvedic Hospital, and...
District Ayurvedic Hospitals. We recommend that Vigiflow software can be used, as per usual pharmacovigilance reporting practice, as this may be linked to the UMC. Pharmacists and Ayurvedic doctors can be mobilized for reporting and management of the software. The scope of the proposed herbal pharmacovigilance center can be expanded to consumer levels in households via consumer awareness programs, such as MedWatch in the USA. This may help address the concerns of consumers’ non-prescriptive Ayurvedic medications at the community level.

The way forward
Globally, herbal medicines are extensively used in health care. Regardless of whether upheld by therapeutic science or basically by many years of use, treatment with herbal medicines will stay prominent. In the quest for an alternative to allopathic medicines and with more evidence-based findings, the use of herbal medicine will increase in the future. Successful implementation of herbal pharmacovigilance is essential for developing reliable information/database on the safety of herbal medicines. It is also essential for the improvement of appropriate guidelines to ensure their safety and effective use. There is an urgent need for educational intervention on adverse reactions with regard to herbal medicine. Continuing education programs are recommended to provide the clinical practitioner’s environment to redesign their insight in this quickly growing public health concern.

Data availability
No data is associated with this article.

References

36. World Health Organization: WHO guidelines on good manufacturing practices (GMP) for herbal medicines. Reference Source
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