

## Challenges in the promotion of herbals as alternative and complementary medicine

Herbals, particularly traditional herbal medicines (codified or non-codified) are of immense value. These have significantly contributed to the development of various medications, and hence have become the focus area of researchers for drug discovery. Eighty per cent of the medications of plant origin are suggested to be based on original ethnopharmacological uses<sup>1</sup>. Paclitaxel (Taxol<sup>®</sup>), the most extensively used drug for breast cancer, was isolated from *Taxus brevifolia* bark. Artemisinin and its derivative artemotil, isolated from *Artemisia annua* and quinine, isolated from *Cinchona succirubra* bark are approved antimalarial drugs. Apomorphine, used to treat Parkinson's disease, is a derivative of morphine, which was isolated from *Papaver somniferum*. Many more effective and safe herbals may be developed as alternative and complementary medicine for different indications with inclusive efforts of the governments, policy makers and technocrats.

China has done outstandingly well in this area, with a large number of patents filed for herbal therapeutics, majority of which are based on traditional Chinese medicine (TCM). Efforts towards integration of TCM in the national health policy were initiated in 1949 with establishment of TCM National Office under the Chinese Ministry of Health. TCM R&D institutions and TCM hospitals occupy a large portion of the budget. For Chinese Materia Medica (CMM), US\$ 4.66 billion was allocated in 2014, double that in 2011 (ref. 2).

During analysis, we could not find patents filed in India by Indian researchers, which are based on documented traditional Indian medicine (TIM). This may be due to lack of awareness among researchers and existence of stringent Indian Patent Laws. The existing Indian Patent Law {u/s 3(p)} presents itself as a bottleneck for the industries to undertake research in herbal drug development, specifically on TIM. However, there is enormous opportunity to develop evidence-based medication using established undocumented/non-codified or modified and value-added TIM and their intellectual property (IP) protection.

Another possible reason for low penetration of TIM in the indigenous and

global market may be less attention paid towards implementation and monitoring of executable schemes and policies at the ground level. Multiple initiatives have been taken by the Indian Government in the arena, including establishment of the Department for Indian Systems of Medicine and Homoeopathy in 1995, renamed as Department of Ayurveda, Yoga, Unani, Siddha, Homoeopathy (AYUSH) in 2003, which is an independent ministry since 2014. Five research councils function under the ministry. These are Central Council for Research in Ayurvedic Sciences (CCRAS), Central Council for Research in Yoga and Naturopathy (CCRYN), Central Council for Research in Unani Medicine (CCRUM), Central Council for Research in Homoeopathy (CCRH), and Central Council for Research in Siddha (CCRS) working through 81 research institutes and centres across India. Surge in the efforts to promote TIM is visible through various international collaborations, setting up of AYUSH Information Cells overseas in Cuba, Hungary, Indonesia, Mauritius and Russia. However, more initiatives are needed such as integration of TIM in education, R&D, resource management and industry collaborations.

Other key challenges towards promotion of indigenous herbal drugs are their standardization and quality control. Also, for most of the codified and non-codified traditional medicines, robust scientific validation and value-addition data in support of their efficacy and safety are lacking.

Numerous reports depict the presence of substandard herbal products, with huge variations in active contents. Panaxoside content of roots and commercial products made of *Panax ginseng* and *Panax quinquefolium* showed huge variations in one such study, with no detectable levels of panaxoside in the tablets and very low concentrations in teas and granules<sup>3</sup>. Withaferin A, the main phytoconstituent of *Withania somnifera* (ashwagandha), commonly used in several ayurvedic formulations, was also reported to show wide variations (as high as 70-fold) among different products<sup>4</sup>. High batch-to-batch and dose-to-dose variations were observed in hyperforin

and hypericin contents in St John's Wort products from different manufacturers in Germany<sup>5</sup>.

The actives in plants are known to vary with season, geography, conditions and time of their collection, processing and storage. Varied content of five ginsenosides (Rg1, Re, Rb1, Rc and Rd) in American ginseng roots collected from different parts of Maryland, USA, was attributed to genotype<sup>6</sup>. Differential distribution of berberine in roots and stem bark in three species of *Berberis* (*B. asiatica*, *B. aristata*, *B. lyceum*) was recorded. Berberine content was found to be higher in roots in comparison to bark<sup>7</sup>. Phenolic compound contents in wild *Calluna vulgaris*, *Sambucus nigra* and *Vaccinium myrtillus* were found to be dependent on variations in altitude<sup>8</sup>. Among the phytochemicals tested, increase in flavonol-3-O-glycosides content was observed with increasing altitude in case of *C. vulgaris* and *S. nigra*, whereas content of anthocyanins present in berries of *S. nigra* and *V. myrtillu* was observed to decrease with increase in altitude.

Effect of harvesting time on the content of quercetin, major flavonoids in *Apocynum venetum* and *Poacynum hendersonii* was analysed. Highest content of flavonoids was observed in summer and lowest in autumn<sup>9</sup>. Content of phytochemicals in whole plant and their accumulation in different parts are well reported to be dependent upon sowing season<sup>10-12</sup>. Herbal products with no or below optimum level of active ingredients will not have the desired effects. Hence while dealing with plant-based medicines, standardization is one of the key steps in the drug development process.

Contamination and adulteration of herbal preparations are other challenges. Several contaminants and residues may get introduced in the herbal medicines or herbal products at different stages of processing and preparation. Possible sources of contaminants include polluted soil and water, during cultivation and growth, manufacturing process, post-harvest processing, transportation and storage, etc.<sup>13</sup>.

Adverse drug reactions due to contamination are important constraints.

Common adulterants used in herbal medicines include synthetic drugs<sup>14</sup>. Corticosteroids-based adulterants are used in herbal medicines to make these more efficacious for treatment of diseases such as systemic lupus erythematosus, rheumatoid arthritis and inflammatory diseases<sup>15,16</sup>. Herb-drug reactions also need to be monitored due to possibility of enhanced or opposite effects of herbs on drugs<sup>17,18</sup>.

In most of the developing countries, traditionally used herbal drugs form an important part of the primary health-care system. Despite this, no uniform legislative controls have been structured at the global level for plant-based medicines. Only 1% studies related to herbal drugs or herbal products is conducted in accordance with the regulatory guidelines for stability testing<sup>19</sup>.

In South Africa, no regulatory guidelines exist for the crude indigenous herbal products. In USA, health claims for herbal products are not allowed and these cannot be sold as drugs. Most natural products in USA are regulated as foods or food additives, while herbs and other botanicals, vitamins and minerals fall under the definition of a dietary supplement according to the Dietary Supplement Health and Education Act, October, 1994.

Herbal medicines in India are regulated by the Drugs and Cosmetics Act (DCA) of 1940 and the Drugs and Cosmetics Rules of 1945. Guidelines issued in 1993 required both allopathic drugs and herbal products to generate clinical trials data. However, herbal drugs and allopathic drugs being dissimilar in respect of their composition and active constituents cannot be scrutinized under similar regulatory guidelines. Ayurveda, Siddha or Unani (ASU) drugs include drugs as described in the classical texts. For these drugs, issue of manufacturing license does not require any data on safety and efficacy, unless it is meant for a new indication. Another class is patent or proprietary medicine, which encompasses ASU drugs with intellectual intervention. Patented medicines encompass products which are different from ASU

medicines. For this category, issue of manufacturing license requires proof of effectiveness, according to relevant protocol for ASU drugs. Under the eighth amendment in Drugs and Cosmetic Rules, 2015, phytopharmaceuticals have been introduced as a new class of drugs and termed as purified and standardized fraction, wherein minimum four bioactives are defined. This may be meant for internal or external application in humans or animals for diagnosis, mitigation, treatment of any disease with parenteral route of administration excluded from the category of these drugs. Requirements for manufacture or import as well as for conducting clinical trials have been clearly defined. It is now mandatory to submit already available information, including published safety and pharmacological studies, reported usage of drugs, history of its use, clinical pharmacological and pharmacodynamics information in case of future marketing of products. Data generated by the applicant such as process of extraction and fractionation, type of formulation applied for and kind of formulation process, animal toxicity data and stability data are also required. Besides, prior to conducting clinical trials, the proposed protocol needs to be submitted<sup>20</sup>.

As the guidelines are evolving across the globe, ethno-medicines as phytopharmaceuticals are finding a place in the drug legislation of most countries. Pharmacovigilance is a crucial area that needs attention. Though requirement of post-marketing surveillance and submission of periodic safety records has been made mandatory in certain countries, implementation is a big challenge. Global consensus with respect to regulations will pave the road for future promotion and inclusion of alternative medicines in the national health-care system and further leveraging the associated benefits.

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