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# Popularization of traditional and complementary medicine: Urging voluminous effort driving towards scientific evaluation of safety and efficacy

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### ABSTRACT

Traditional medicines are widely used in developing countries with fast gaining popularity all over the world. Traditional medicine practices has long historical background that passes on from generation to generation. The quantity and quality, safety and efficacy of traditional medicine has become a worldwide concern emphasizing the need to develop harmonized international standards. The global market for herbal remedies is about \$83 billion and growing at 10 to 20 percent yearly with the top global players like Germany, Asia, Japan, Europe and North America.

Traditional therapies have a popular perception lower adverse effects rate as consumers perceive that natural sourced products are less likely to cause problems. The common causes of herbal product related adverse reaction occurrence are use toxic herbs, overdose, drug–herb interactions and idiosyncratic reactions. Herbal are mostly used over the counter without knowledge or advice of practitioner rising safety concern. Quality issues of traditional products are due to improper processing, adulteration, misidentification, missing of one or more herbs in a product, substitution, inclusion of prescription drugs, contamination and variability in active ingredient. Scientific study to assess safety and efficacy, composition, dosage form requirements are need of the time.

Regulations governing the safety, quality and efficacy of traditional and complementary therapies vary widely from country to country and many countries do not have formal system for traditional and complementary medicine registration.

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Implementation of good manufacturing practice in cultivation, harvesting and processing along with chromatographic fingerprinting will greatly contribute to quality control of traditional medicines. Rigorous research is required for preclinical safety-efficacy, toxicology and clinical trials of traditional and complementary medicine. Boosting research with availability of funds are a major issue. Credibility of traditional and complementary will depend on development of evidence base approval system by encouraging spontaneous reporting, implementing active pharmacovigilance and clinical safety monitoring system.

## Introduction

Use of traditional medicine is gaining popularity not only in developing countries but throughout the globe. WHO describes traditional medicine as "Traditional Medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness." The complementary or alternative medicine refer to a broad set of health care practices that are part of a country's own tradition and mostly are not integrated into the dominant health care system [1]. Unlike the conventional medicine the traditional medicine practices has long historical background based on experience passed on from generation to generation. At the International Conference on Traditional Medicine for South-East Asian Countries in February 2013, the WHO Director-General, Dr Margaret Chan, stated that "For many millions of people, herbal medicines, traditional treatments, and traditional practitioners are the main source of health care, and sometimes the only source of care. This is care that is close to homes, accessible and affordable. It is also culturally acceptable and trusted by large numbers of people" [2].

Traditional medicine practices greatly vary in different cultures and regions and are influenced by culture, history, tradition, geography, personal attitudes and philosophy. From the past centuries the practice of

traditional medicines has been passed on to generations without a parallel development of international standards and appropriate methods for quality evaluation. In the light of the current strictly controlled pharmaceutical era, scientific research is needed to provide proper evidence of its safety and efficacy. Voluminous expansion in the use of traditional medicine has eventually raised the safety, efficacy and quality concerns for both health authorities and the public. Traditional medicine with proven quality, safety and efficacy will eventually contribute to the goal of ensuring health care access to a wide population. Many countries now recognize the need to develop a cohesive and integrative approach to access traditional and complementary medicine in a trustworthy and cost effective manner [3].

The quantity and quality of the safety and efficacy data on traditional medicine are far from sufficient to meet the criteria needed to support its use worldwide. All these aspects of traditional medicine practice globally are urging the need to take over the hilarious task of developing harmonized international standards.

## Global market for traditional remedies

Traditional and complementary therapies use herbs, animal parts, minerals or homeopathic remedies. Herbs are used as crude materials, preparations and finished products containing plant based therapeutically active ingredients. Therapeutic interventions like acupuncture, massage, heat, yoga, meditation are also practiced. According to WHO, nearly 80% of African and Asians use traditional medicine as part of primary health care signifying its economic importance [4]. Traditional medicine practices have greater accessibility and cultural acceptance in low and middle income countries due to comparative low cost and easy availability. People of developed countries mostly use traditional medicine for preventing disease, maintaining wellness or complementing conventional care for chronic diseases.

The global market for herbal remedies is about \$83 billion and growing at 10 to 20 percent a year. The global herbal pharmaceutical industry contributes \$44 billion and beauty products make up the remaining \$14 billion. The top global players in herbal medicines market is Germany (28%), Asia (19%), Japan (17%), France (13%), rest of Europe (12%) and North America (11%). The Asian market is estimated to be worth about \$9 billion and is expected to continue. 30% of Indian health care market is controlled by

Ayurvedic medicine manufacturers and other traditional products account for the remaining 10% of the market. China has a strong hold on history in herbal and botanical products with sale estimated to be about \$3.5 billion. The market size of Japan's herbal market was estimated to be around \$2.5 billion.

In 2008, herb and botanical sales in US were at \$4.8 billion, with an estimated growth rate of nearly 4%. Raw herbal material sales in US are declining by 41% since 1999, mostly imported from China and India. The European market for herbal supplements and herbal medicines is currently worth \$7.4 billion. Germany is the largest European market, with a 27% share, followed by France (24%), Italy (12%) and the U.K (9%). Uncertain regulatory environment and pending legal action related to the EU Food Supplement Directive has stifled herbal product market development in UK. The fastest-growing categories of herbal medicines include weight loss products and sport nutrition. In addition to low-dose vitamins, the food supplement category includes products such as guarana, chitosan, fibers, fish oil, borage oil, lycopene, lutein, evening primrose oil, lecithin and *Aloe vera* [5].

### Safety issues of traditional medicine

Herbal drug market has changed significantly over the past decade with the advent of new segments like functional foods and cosmeceuticals. Herbal manufacturer is harnessing the current global consumer interest in natural and functional foods, such as botanical alternatives to animal-sourced omega 3 fatty acids from fish, artificial coloring agents, new varieties of fiber and beauty foods. The growth and development of the herbal botanical drug market is not as deserved due to requirements of long product research and development time and drug registration formalities.

Traditional therapies have a common and popular perception of having lower rate of adverse effects compared with conventional therapies that encourage some patients to choose an herbal medication over a conventional medication specifically to avoid adverse effects. Although consumers may perceive herbal products as natural and therefore less likely to cause problems, these products are not without risk and are not necessarily safer than conventional pharmaceuticals [6]. The causes of adverse reactions associated with herbal medicines are due to use of inherently toxic herbs, overdose of herbs, drug-herb interactions and idiosyncratic reactions such as aller-

gies. Most countries have no adverse drug reaction surveillance (pharmacovigilance) system for herbal medicines which further prevented the information of herbal drug toxicities coming out in public notice. A prime concern giving out occurrence of adverse reactions are over the counter use of herbal products by consumers often without knowledge or advice of practitioner. Consumers and practitioners are not adequately informed about potential adverse effects, drug interactions and use directives of herbal medicines. Drug-herb interactions related adverse actions can be prevented through improved communication between patients and health care providers and better consumer information.

The occurrence of undesirable side effects though is less frequent with herbal medicines, but well-controlled, randomized clinical trials have revealed that they also exist. Incorrect usage of herbal medication is also responsible for fatal outcomes as most of the chronic disease patients use herbal products for long time. The long-term use of kava kava (*Piper methysticum*) is associated with serious cases of liver damage, *Ginkgo biloba* cause excessive bleeding during surgery, aristolochic acid, from the plant *Aristolochia* showed relationship with kidney failure, *Ma huang* (*Ephedra sinica*) contains ephedrine led to severe respiratory effects and deaths [7-8]. Herbal medicine should be adopted by appropriate dosage and course of treatment and for adapted syndrome, rather than unrestricted abusing. Overdosage and very long course of treatment are bound to safety problems. Many herbal product container have inadequate or unclear information about usage or possible adverse effects leading to improper use by consumers due to lack of strict labeling regulation of herbal preparations.

### Quality issues of traditional medicine

Production and manufacturing of herbal medications are not under strict control in larger segment of the world causing quality problems. The primacy reason of herbal quality issues are improper processing, adulteration, misidentification of ingredients, missing of one or more herbs from a poly herbal product, substitution of one herb with another, inclusion of prescription drugs, contamination and variability in the amount of active ingredient. Medicinal plants collected from the wild may be contaminated by other species or plant parts through misidentification, accidental contamination or intentional adulteration. Inadvertent contamination by microbial or chemicals

during the production stages can also affect the quality, safety and efficacy. Contamination with mycotoxin, heavy metals, fumigation agents, microbial toxins in toxic concentrations are of high concern in developed countries<sup>[10-12]</sup>. There are cases of herbal weight loss product recall from USA due to addition of unlabeled prescription drug and chemicals that can cause rise in blood pressure and cancer<sup>[13]</sup>.

More than two-third of all drugs discovered in the previous quarter-century were derived from natural products, i.e., aspirin from white willow tree, paclitaxel from Pacific yew tree<sup>[9]</sup>. Though many of the pure pharmaceutical drugs used therapeutically now-a-days were originally derived from plant sources, they are no longer isolated from the plant sources but synthetically produced. Isolation and purification of phytocompounds is a tedious and costly procure and it is also very difficult to get a single pure isolated phytocompound. Traditional herbal industry till now mostly uses poly herbal products to cure a particular ailment. Quality control of poly herbal products possess a troublesome challenge to the scientific community as it is very tiresome to develop a product specific monograph for separation, isolation and identification. Addition of prescription drug can be analysed by conventional analytical procedure but substitution or not at all adding a particular herb and bioactive ingredient variation can only be identified by a well specified monograph.

### **Implementing regulation on traditional and complementary medicine**

Ever increasing popularity of traditional medicine is adjuring the development of comprehensive regulation and legislation. Depending on the technological advancement of a country the herbal remedies ranges from medicinal tea, crude power, tablets to concentrated, standardized extracts and enriched, isolated constituents produced in modern pharmaceutical facilities. To be registered as medicines, herbal products must undergo scientific study to assure their safety and efficacy, proper composition, dosage form and claimed indications. Policies, laws, and regulations governing the safety, quality, and efficacy of traditional and complementary therapies vary widely from country to country. Most developing countries do not have formal regulation or have a weak regulatory infrastructure to control traditional and complementary medicine and do not have registration system of products like that of conventional

medicines. Reluctant regulatory guideline does not require evidence of quality, efficacy and safety before marketing of traditional medicinal products. Lack of regulations on quality standards and evaluation for safety and efficacy of these products is resulting in marketing of unsafe and ineffective products. The Chinese and Indian governments is promoting traditional medicine to strengthen primary health care in remote areas where as Africa is looking forward to use local traditional resources as integrated part of minimal health care packages on the other hand Europe is imposing licensing and creating standards for quality control<sup>[14]</sup>. In US, herbal products are regulated as foods rather than as medicines and manufacturers are not required to conduct safety or efficacy tests on their products.

The differential approach in recognizing and classifying traditional preparations in the countries lacking a established system for traditional medicine regulation can be harmonized by developing an international framework for evaluating and regulating these products<sup>[15]</sup>. WHO has developed strategies to address these challenges through the publication of the series of WHO Traditional Medicine Strategy: 2002–2005 to 2014-2023. The 2002-2005 strategy includes four major objectives: (1) framing government policy; (2) ensuring safety, efficacy, and quality; (3) enhancing access; and (4) promoting proper use of traditional and complementary medicines<sup>[16]</sup>. The current 2014-2023 strategy has two key goals, i.e., to support Member States in harnessing the potential contribution of traditional and complementary medicines to health, wellness and people centred health care and to promote the safe and effective use through regulation of products, practices and practitioners. These goals will be reached by implementing three strategic objectives: 1) building the knowledge base and formulating national policies; 2) strengthening safety, quality and effectiveness through regulation; and, 3) promoting universal health coverage by integrating traditional and complementary medicine services and self-health care into national health systems<sup>[2]</sup>.

In Europe, the Traditional Herbal Medicinal Products Directive is having a positive impact allowing access to the market via a simplified registration procedure without having to carry out unnecessary safety and efficacy assessments for products having a long history of traditional use<sup>[14]</sup>. There is no inherent prejudice in Europe against molecular complexity of plant substances rather, it is regarded as single substances. The costs and time required to approve herbal medicines safety and effica-

cy is less in Europe for substances that have a long history of use and can be approved under the “doctrine of reasonable certainty.” The European Economic Community (EEC) guidelines outline standards for quality, quantity, production and labelling of herbal remedies. In Japan, China, and India, herbal preparations are mostly used as dried and powdered whole herbs or herb extracts in liquid or tablet form. In 1984, the People’s Republic of China implemented the Drug Administration Law, considering traditional herbal preparations as “old drugs” and, except for new uses, were exempt from testing for efficacy or side effects. Traditional Japanese medicine, called kampo, is similar to Chinese traditional medicine. In 1988, the Japanese herbal medicine industry established regulations to manufacture and control the quality of products in kampo medicine<sup>[17]</sup>. The Indian Pharmacopoeia (2010) contains monographs of herbs is to provide qualitative and quantitative standards of quality for use as food item/ food ingredient/ food supplement/ nutraceuticals, as a drug, and / or as an ingredient in cosmetics. IP regarded each herb as one active substance, irrespective of the knowledge about the active constituents of the herb is available or not<sup>[18]</sup>.

### **Research promotion for proven safety and efficacy of traditional medicine**

Consumers are attracted to traditional and complementary medicines as it is assumed to be effective and almost free of risk but scientifically it cannot be stated with confidence due to insufficient evidence for conducting reliable risk benefit analysis<sup>[19]</sup>. Many pre-clinical and clinical studies carried out in traditional medicines are being published in the literature, but the level of evidence available in the long standing clinical use of traditional medicine does not generally meet the internationally accepted standards of clinical trials of new drugs.

Like the conventional drugs, the quality of herbal medicine also depends on the amount and range of medicinally useful or active constituents present. The correct identification of a plant with reference to its accepted scientific name(s) is a primary step in the quality assurance process, as a single common name may often refer to different plant species, with potentially dangerous consequences. Implementation of good manufacturing practice in cultivation, harvesting and processing will definitely influence the quality of herbal medicines. Polyherbal formulations usually comprising mixture of herbal materials defined in a formula contains hundreds of components. Testing for the content of a single component may therefore not reflect the quality, safety and efficacy

of a herbal preparation. Chromatographic fingerprinting methods such as high-performance thin layer chromatography and high-performance liquid chromatography are the most practical ways for defining the chemical profiles. The quality testing system for traditional medicine products should have provisions to detect any mislabelling, misidentification, variation between batches and presence of undeclared components<sup>[20]</sup>.

Rigorous research is required that certainly should not confine to preclinical efficacy study, toxicological study, clinical trials only but also post marketing surveillance studies for defining the safety of traditional and complementary medicine<sup>[21]</sup>. Boosting research in the field of traditional medicine is required to specify both benefit and risk with accurate scientific evidence. Availability of funds are scarce for traditional medicine research compared with other specialization of medical science<sup>[22]</sup>. Governments and other funding bodies usually allocate health resources on the basis of existing evidence. Research on traditional medicine requires widespread recognition that will definitely attract high caliber scientists with expertise in this presently underdeveloped sector. Adequate research funds must be made available to fuel this process.

### **Conclusion**

All countries should have well defined regulatory framework in place to review and monitor traditional and complementary medicines, including a coordination agency, a national advisory committee, and a pharmacovigilance system. Countries that already have a strong pharmaceutical regulatory structure in place should modify their existing systems to adopt herbal medications, and countries that lack regulatory standards should work toward setting up a national system that encompasses both pharmaceuticals and traditional and complementary medicines. Many pharmacologically active herbs are needed to be registered as herbal medicinal products. The herbal and traditional medicine market around the world are still far from realizing their full potential. New phytochemicals and new indications for known phytochemicals are still to be discovered. Phytochemicals with proved efficacy and their claim substantiation is expected to have the highest impact on new product development in the herbal and botanical market. This, of course, will require a huge investment in the safety and efficacy study of new products and then marketing. Credibility of traditional and complementary will depend on

development of evidence base approval system with safety and efficacy assessment. Consolidation of existing national and international studies and supporting new research to fill gaps will work towards fulfillment of this aim. Encouraging spontaneous reporting and implementing active pharmacovigilance will be very effective in identifying therapeutically relevant safety issues. Implementation of clinical safety monitoring system for traditional medicines along with herbal pharmacovigilance system is of critical importance for promoting safe use of traditional medicines.

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