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R E S E A R C H A R T I C L E

Herbal Medicine- A Growing Field with a Long Tradition and Their Regulatory Requirements

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A B S T R A C T

The use of herbal drugs for the prevention and treatment of various health ailments has been in practice from time immemorial. Generally it is believed that the risk associated with herbal drugs is very less, but reports on serious reactions are indicating to the need for development of effective marker systems for isolation and identification of the individual components. Standards for herbal drugs are being developed worldwide but as yet there is no common consensus as to how these should be adopted. Standardization, stability and quality control for herbal drugs are feasible, but difficult to accomplish. Further, the regulation of these drugs is not uniform across countries. There are variations in the methods used across medicine systems and countries in achieving stability and quality control. The present study attempts to identify the evolution of technical standards in manufacturing and the regulatory guideline development for commercialization of herbal drugs.

Key words: Herbal drugs, quality control, regulatory guideline etc.

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1. Introduction

Traditional medicine is "the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, used in the maintenance of health and in the prevention, diagnosis, improvement or treatment of physical and mental illness" (World Health Organization, http://www.who.int/topics/traditional_medicine/en/). There are many different systems of traditional medicine, and the philosophy and practices of each are influenced by the prevailing conditions, environment, and geographic area within which it first evolved (WHO 2005), however, a common philosophy is a holistic approach to life, equilibrium of the mind, body, and the environment, and an emphasis on health rather than on disease. Generally, the focus is on the overall condition of the individual, rather than on the particular ailment or disease from which the patient is suffering, and the use of herbs is a core part of all systems of traditional medicine.

Traditional Chinese medicine (TCM) is an important example of how ancient and accumulated knowledge is applied in a holistic approach in present day health care. TCM has a history of more than 3000 years. The book The Devine Farmer's Classic of Herbalism was compiled about 2000 years ago in China and is the oldest known herbal text in the world, though the accumulated and methodically collected information on herbs has been developed into various herbal pharmacopoeias and many monographs on individual herbs exist. Diagnosis and treatment are based on a holistic view of the patient and the patient's symptoms, expressed in terms of the balance of yin and yang. Yin represents the earth, cold, and femininity, whereas yang represents the sky, heat, and masculinity. The actions of yin and yang influence the interactions of the five elements composing the universe: metal, wood, water, fire, and earth. TCM practitioners seek to control the yin and yang levels through 12 meridians, which bring and channel energy (Qi) through the body. TCM is a growing practice around the world and is used for promoting health as well as for preventing and curing diseases. TCM encompasses a range of practices, but herbal medicine is a core part. Three of the top-selling botanical products, namely Ginkgo biloba, Allium sativum (garlic), and Panax ginseng, can be traced back to origins in TCM and are today used to treat various diseases.

Over the past 100 years, the development and mass production of chemically synthesized drugs have revolutionized health care in most parts of the word. However, large sections of the population in developing countries still rely on traditional practitioners and herbal medicines for their primary care. In Africa up to 90% and in India 70% of the population depend on traditional medicine to help meet their health care needs. In China, traditional medicine accounts for around 40% of all health care delivered and more than 90% of general hospitals in China have units for traditional medicine (WHO 2005). However, use of traditional medicine is not limited to developing countries, and during the past two decades public interest in natural therapies has increased greatly in industrialized countries, with expanding use of ethnobotanicals. In the United States, in 2007, about 38% of adults and 12% of children were using some form of traditional medicine. According to a survey by the National Center for Complementary and Alternative Medicine, herbal therapy or the usage of natural products other than vitamins and minerals was the most commonly used alternative medicine (18.9%) when all use of prayer was excluded. A survey conducted in Hong Kong in 2003 reported that 40% of the subjects surveyed showed marked faith in TCM compared with Western medicine. In a survey of 21,923 adults in the United States, 12.8% took at least one herbal supplement and in another survey, 42% of respondents used dietary or nutritional supplements, with multivitamins and minerals most commonly used, followed by saw palmetto, flax, garlic, and Ginkgo, at the time of the interview.

2. Herbal Medicine and the Aging Population

Average life expectancy at birth has increased from around 41 years in the early 1950s to approaching 80 years in many developed countries. Consequently, the percentage of elderly people (65 years and above) in our populations is increasing. The graying of our populations brings an increasing burden of chronic age-related disease and dependency. Aging is associated with a progressive decline in physiological function and an increased risk of pathological changes leading to cancer, cardiovascular disease, dementia, diabetes, osteoporosis, and so on. Lifestyle factors such as nutrition or exercise play an important role in determining the quality and duration of healthy life and in the treatment of chronic diseases It is most likely that there is no one cause of aging, and different theories of aging have been suggested over the years. Genetic factors are undoubtedly important, but among all the metabolic theories of aging, the oxidative stress theory is the most generally supported theory This theory postulates that aging is caused by accumulation of irreversible, oxidation-induced damage (oxidative stress) resulting from the interaction of reactive oxygen species with the DNA, lipid, and protein components of cells. However, even if the aging process itself is found to be unrelated to oxidative stress, highly prevalent chronic age-related diseases all have increased oxidative stress. Antioxidants in herbs may contribute at least part of their reputed therapeutic effects. With the growing popularity of herbal medicine, the "traditional" ways of identification and preparation of herbs need to be replaced with more accurate and reproducible methods so as to ensure the quality, safety, and consistency of the product. Given the market value, potential toxicity and increasing consumer demand, particularly in the sick and elderly members of our populations, regulation of production and marketing of herbal supplements and medicines require attention.

3. Herbal Medicines: Challenges and Regulations

WHO has recognized the important contribution of traditional medicine to provide essential care (World Health Organization). In 1989, the U.S. Congress established the

Office of Alternative Medicine within the National Institutes of Health to encourage scientific research in the field of traditional medicine, and the European Scientific Cooperative on Phytotherapy (ESCOP) was founded in 1989 with the aim of advancing the scientific status and harmonization of phytomedicines at the European level. This led to an increase in investment in the evaluation of herbal medicines. In the United States, the National Center for Complementary and Alternative Medicine at the National Institutes of Health spent approximately US$33 million on herbal medicines in the fiscal year 2005; in 2004, the National Canadian Institute committed nearly US$89 million for studying a range of traditional therapies. While this scale of investment is low compared to the total research and development expenses of the pharmaceutical industry, it nevertheless reflects genuine public, industry, and governmental interest in this area.

With tremendous expansion in the interest in and use of traditional medicines worldwide, two main areas of concern arise that bring major challenges. These are international diversity and national policies regarding the regulation of the production and use of herbs (and other complementary medicines) and their quality, safety, and scientific evidence in relation to health claims.

4. Research Needs

Research needs in the field of herbal medicines are huge, but are balanced by the potential health benefits and the enormous size of the market. Research into the quality, safety, molecular effects, and clinical efficacy of the numerous herbs in common usage is needed. Newly emerging scientific techniques and approaches, many of which are mentioned in this book, provide the required testing platform for this. Genomic testing and chemical fingerprinting techniques using hyphenated testing platforms are now available for definitive authentication and quality control of herbal products. They should be regulated to be used to safeguard consumers, but questions of efficacy will remain unless and until adequate amounts of scientific evidence accumulate from experimental and controlled human trials. Evidence for the potential protective effects of selected herbs is generally based on experiments demonstrating a biological activity in a relevant in vitro bioassay or experiments using animal models. In some cases, this is supported by both epidemiological studies and a limited number of intervention experiments in humans. In general, international research on traditional herbal medicines should be subject to the same ethical requirements as all research related to human subjects, with the information shared between different countries. This should include collaborative partnership, social value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for the subjects. However, the logistics, time, and cost of performing large, controlled human studies on the clinical effectiveness of an herb are prohibitive, especially if the focus is on health promotion. Therefore, there is an urgent need to develop new biomarkers that more clearly relate to health (and disease) outcomes. Predictor biomarkers and subtle but detectable signs of early cellular change that are mapped to the onset of specific diseases are needed. Research is needed also to meet the challenges of identifying the active compounds in the plants, and there should be research-based evidence on whether whole herbs or extracted compounds are better. The issue of herb–herb and herb–drug interactions is also an important one that requires increased awareness and study, as polypharmacy and polyherbacy are common. The use of new technologies, such as nanotechnology and novel emulsification methods, in the formulation of herbal products, will likely affect bioavailability and the efficacy of herbal components, and this also needs study. Smart screening methods and metabolic engineering offer exciting technologies for new natural product drug discovery. Advances in rapid genetic sequencing, coupled with manipulation of biosynthetic pathways, may provide a vast resource for the future discovery of pharmaceutical agents. This can lead to reinvestigation of some agents that failed earlier trials and can be restudied and redesigned using new technologies to determine whether they can be modified for better efficacy and fewer side effects. For example, maytansine isolated in the early 1970s from the Ethiopian plant Maytenus serrata, looked promising in preclinical testing but was dropped in the early 1980s from further study when it did not translate into efficacy in clinical trials; later, scientists isolated related compounds, ansamitocins, from a microbial source. A derivative of maytansine, DM1, has been conjugated with a monoclonal antibody and is now in trials for prostate cancer.

5. International Regulatory Overview

India:

Herbal drugs are regulated under the Drug and Cosmetic Act (D and C) 1940 and Rules 1945 in India, where regulatory provisions for Ayurveda, Unani, Siddha medicine are clearly laid down. Department of AYUSH is the regulatory authority and mandate that any manufacture or marketing of herbal drugs have to be done after obtaining manufacturing license, as applicable.

The D and C Act extends the control over licensing, formulation composition, manufacture, labeling, packing, quality, and export. Schedule "T" of the act lays down the good manufacturing practice (GMP) requirements to be followed for the manufacture of herbal medicines. The official pharmacopoeias and formularies are available for the quality standards of the medicines. First schedule of the D and C Act has listed authorized texts, which have to be followed for licensing any herbal product under the two categories:

- ASU drugs
- Patent or proprietary medicines.

Malaysia:

Herbal products in Malaysia fall under the category of regulated products. Any marketer intending to place the herbal products in the market require to register the productfirst. The applicant is required to be registered with the Malaysia Registrar of Business or Suruhanjaya Syarikat Malaysia under two classifications:

- Traditional products
- Health supplements.

While the authorities mandate only labeling "traditionally used for" in front of any claim made on the traditional product, only those functional claims, which are listed by the authority are allowed in supplements.

Philippines:

The herbal medicines are regulated in the Philippines as traditionally used herbal products. The regulators require that the preparations from plant materials, whose claimed application is based only on traditional experience of long usage, which should be at least five or more decades as documented in medical, historical, and ethnological literatureare permitted to be marketed under this category.

The Bureau of Food and Drugs (BFAD), who are the regulators in the country, mandate registration of the traditionally used herbal products before manufacture, import or market. The extent of control of BFAD includes the brand names of the traditional herbal products as well, and their prior clearance is required, before filing for product registration. Authentication of the plant specimen needs to be obtained from the Philippine National Museum or any BFAD recognized taxonomist, and for imported products, the certificate of authenticity of the plants from the authorized government agency of the country of origin is accepted. The quality control requirements further lay down that the pharmacopoeial standards. BFAD further mandates that product indications should not require supervision by a physician.

Nigeria:

In Nigeria, the trade of herbal products is regulated by National Agency for Food and Drug Administration and Control (NAFDAC) who has classified these products as "Herbal Medicines and Related Products." Premarketing registration of herbal medicines and related products is mandatory in Nigeria. All advertisements require a preclearance from NAFDAC. No advertisement can be made as a cure for any disease conditions listed in "Schedule 1" to the Food and Drug Act 1990.

Saudi Arabia:

Herbal products are classified in Saudi Arabia as traditional products. They are allowed if they have at least 50 consecutive years of traditional use. Their dose and the method of preparation must be same as those used, traditionally. According to the evidence provided, they may fall under the sub-categories:

- Pharmacopoeial evidence for traditional products
- Nonpharmacopoeial evidence for traditional products.

For the former, the medicinal ingredients, quantity, recommended dose, route of administration, duration of use, dosage form, directions of use, risk information should be same as the Pharmacopoeia and the method of preparation must be traditional.

For the latter category, any two independent references must be provided to supplement the evidence supporting the safety and efficacy of the product, from clinical studies, pharmacopoeias, and textbooks, references, peer-reviewed published articles, data from nonclinical studies on pharmacokinetics, pharmacodynamics, toxicity information, reproductive effects, and the potential genotoxicity or carcinogenicity of an ingredient or information based on previous marketing experience of a finished product.

Australia:

Therapeutic Goods Administration, the regulatory agency of Australia, regulate herbal products under the category of complementary medicine. Ayurveda medicine, traditional Chinese medicine, and Australian indigenous medicines are all covered under this category. Complementary medicines which do not require medical supervision are permitted and have to be entered on the Australian Register for Therapeutic Goods (ARTG) before marketing. The low-risk medicines require to be listed while the medicines for comparatively higher risk therapeutic conditions require registration on the ARTG. Only evidence-based claims which are entered on the ARTG are allowed.

United States of America :

The botanical products are classified as a drug, food or a dietary supplement by the United States Food and Drug Administration on the basis of the claims or end use. A product that is used to prevent, diagnose, mitigate, treat or cure a disease would fall under the category of drug. If the intended use of a botanical product is to affect the structure or function of the human body, it may be classified as either a drug or a dietary supplement. As per FDA, the drug must be marketed under an approved New Drug Application (NDA). FDA regulates the dietary supplements under the Dietary Supplement Health and Education Act of 1994. These do not require premarket approval and it's the responsibility of the marketer to ensure the safety and labeling compliance of their products with the regulations. The claims need to comply with the regulatory guidelines issued by the FDA. The manufacturing of dietary supplements should be done as per the current GMP for dietary supplements.

Canada:

Since January 1, 2004, Health Canada regulates herbal remedies and traditional medicines such as Ayurveda medicine, under the natural health products regulations. The regulations mandate that a manufacturer, packer, labeler or importer need to have a prior registration with Health Canada before commencing any such activity. The process involves registration of the manufacturing site/s along with the products. Complete data on product composition, standardization, stability, microbial and chemical contaminant testing methods and tolerance limits, safety and efficacy along with ingredient characterization, quantification by assay or by input needs to be submitted to Natural Health Product Directorate (NHPD). The authority mandate that NHPs must comply with the contaminant limits and must be manufactured as per the GMP norms.

European Union:

The European Medicine Agency have laid down two ways of registration of herbal medicinal products: (1) A full marketing authorization by submission of a dossier, which provides the information on quality, safety and efficacy of the medicinal products including the physicochemical, biological or microbial tests and pharmacological, toxicological and clinical trials data; under directive 2001/83/EC. (2) For traditional herbal medicinal products,

which do not require medical supervision, and where evidence of long traditional of use of medicinal products exists, and adequate scientific literature to demonstrate a well-established medicinal use cannot be provided, a simplified procedure under directive 2004/24/EC exists.

The evidence of traditional use is accepted as evidence of efficacy of the product. However, authorities may still ask for evidence to support safety. Quality control requirements require physicochemical and microbiological tests to be included in the product specifications. The product should comply to the quality standards in relevant pharmacopoeias of the member state or European Pharmacopoeia. The bibliographic evidence should support that the product has been in medicinal use for at least 30 years out including at least 15 years within the European community. The application for traditional use registration shall be referred to the Committee for Herbal Medicinal Products, if the product has been in the community for less than 15 years, but otherwise qualifies for the simplified registration procedure under the directive.

6. Conclusion

The legal status and the practice of use of herbal drug products vary significantly from one country to another thus making it difficult for the free circulation of such products. European regulations are most comprehensive among most of the global regulations for herbal medicinal products. FDA guidelines on botanical drug products established New Drug Application (NDA) route parallel closely the route followed for a synthetic new chemical entity. Indian regulations are also developing vis a vis to global regulations for herbal drug products. Indian regulations are still at nascent stage when compared to regulations of Europe and US. Harmonization of regulations, like that in European Countries could overcome the barrier for efficient trade as well as uniform standards for herbal medicinal products.

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