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SCOPE FOR HARMONISATION OF HERBAL MEDICINE REGULATIONS

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ABSTRACT: Herbal Medicinal Products are gaining acceptance among people across the world due to rising awareness of lifestyle diseases and improper food habits. During the latter part of the twentieth century, increasing interest in self-care resulted in enormous growth in the popularity of traditional healing modalities, including the use of Herbal remedies. Side effects caused by the use of modern medicines are driving consumers towards herbal medicines and their supplements and this is driving the growth of Herbal Medicines across the world. Herbal Medicines, when sold commercially, should comply with country-based regulations concerning safety, quality, and efficacy. At present regulations for herbal medicines differ country-wise. Due to this, herbal medicine companies cannot manufacture a standard product for the global market. Hence a concerted effort should be undertaken by global regulatory authorities and agencies like WHO to establish a uniform and harmonized regulation for herbal medicines. In this paper, we highlighted various challenges and constraints in manufacturing as well as the marketing of herbal medicinal products across the globe.

INTRODUCTION: [1, 2, 3, 4, 5] From the good olden days, Herbal medicines are manufactured and marketed as Ayurveda, Siddha, and Unani, *etc*., in India. Consumers are accepting herbal medicines and they are now used for the prevention and curation of ailments and as an alternative to the allopathic system of medicine. As herbals are already an integral part of patient health care, the rise in the awareness of advantages of their usage drove their demand globally as well as the rise in the commercialization of herbals. The sudden scale of increased consumption of herbal medicine globally gave rise to concerns for efficacy, safety, and quality concerns and this necessitated the presence of robust regulations for their control.

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Innovative techniques like active compounds identification, authentication, fingerprinting, genetic sequencing, and manipulation of biosynthetic pathways led to the discovery of new products with augmented effectiveness clinically, which results in reduced side effects. Regulatory bodies of the member countries and WHO are working to set up a harmonized legislation for Herbal Medicines by way of planning proper policies, standardization classification, regulations to protect intellectual property and improved pharmacovigilance. ASEAN and countries like the USA, Canada, the United Kingdom (UK), member countries of the European Union (EU) already have well-laid regulations for herbal medicines and are now collaborating with WHO for setting a common framework for herbal medicine regulation.

An Overview of Herbal Regulations across India, USA and EU:

India: [6, 7, 8, 9, 10] In India, Herbal medicines are regulated by the Drug and Cosmetic Act (D and C)

1940 and Rules 1945, in which provisions for regulation of Ayurveda, Unani, and Siddha medicine are specified. It also provides for control of quality, composition, licensing, manufacture, formulation, labeling, packing, and export of herbal medicines.

Herbal medicines are regulated by the Department of AYUSH and it mandates that any manufacturing or marketing for herbal drugs has to be done only after completion of approval of the application for a license to manufacture the specified herbal medicine. Good manufacturing practice requirements for the manufacture of herbal medicines are laid down in the Schedule "T" of the D and C act.

Rules, Regulation & Governing Body in India: Traditional Indian System of Medicine (ISM) was recognized in 1959, by Govt. of India, and updates were made to the Drug and Cosmetic Act accordingly. Over the duration of time, several expert working groups (EWG) for different ISM were formed promptly, and the first such EWG was formed in 1962. A separate chapter related to Ayurveda, Siddha, and Unani drugs was created by act 13 of 1964. In the years 1983, 1987, 1994, and 2002 the act was further modified. Guidelines for the evaluation and analysis of drugs under ISM were given under D and C Rules 1945 in 2006 and 2008. In the year 1970, the Central Council of Indian Medicine (CCIM) is constituted, which framed and implemented different regulations as also the curricula and syllabi for ISM (*i.e.*, Ayurveda, Siddha, and Unani). Sowa Rigpa system of medicine was incorporated in the CCIM in the year 2012. To develop the ISM, in 1995, the Department of Indian Medicine and Homeopathy (ISM & H) was formed. Which was renamed as Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH) in 2003 and 2014, separate ministry of AYUSH were formed.

In 2009 certification scheme for AYUSH drug products was introduced by the Department of AYUSH in collaboration with QCI. Concerns were raised over some time about the quality of AYUSH products about their quality, efficacy, and safety. A new scheme for voluntary certification of AYUSH products in collaboration with QCI has been initiated to answer these concerns.

The department of AYUSH has two levels of the certification scheme. The primary one is AYUSH Standard Mark, which abides by the domestic regulatory requirements; and the secondary one is AYUSH Premium Mark, which compiles the following options; Option A: Based on WHO Guidelines specified in the Certification Criteria document, it should comply with the GMP requirements and levels of contaminants. Option B: Option B is more rigid when compared to option A that it should comply with the regulatory requirements of any importing country.

Ayush and Health Policy: In India, the Department of AYUSH focuses on education, regulation, development, growth of ISM, and overall governance. This consists of several autonomous bodies and few subordinate offices such as national institutes, research councils, academies, professional councils, pharmacopeia laboratories, and hospitals. National Policy on Indian Systems of Medicine & Homoeopathy was introduced in the year 2002. This policy's key objective is to exploit the AYUSH in achieving good health and promote healthcare to people in terms of safe and effective services and drugs that meet the Pharmacopoeial standards which meet the quality of AYUSH products.

To oversee the manufacturing and sale of Ayurveda, Siddha, and Unani (ASU) medicine, there are numerous legislative and administrative measures in India. The assistance for regulations of manufacturing, packaging, labeling, and sale of ASU drugs was laid down in chapter IVA of Drugs & Cosmetics Act, 1940. For the advancement of ASU drugs, occasional revisions must be executed, and the recent amendments to this chapter IVA were done in March 2013.

In the regulation of the ASU drugs, a distinct Ayurveda, Siddha, and Unani Technical Advisory Board (ASUDTAB) were established to deal with and guide the authorities on the technical concerns. In India, Ayurveda, Siddha, and Unani Drugs Consultative Committee (ASUDCC) were formed to gain conformity with the administration of Drugs & Cosmetics Act, 1940. For ensuring safety and quality of polyherbal/herbomineral preparations, the Council for Scientific & Industrial Research (CSIR) laboratories, Central Council for Research

in Unani Medicine (CCRUM), Pharmacopoeial Laboratories, Central Council for Research in Ayurveda and Siddha (CCRAS) laboratories, and some other laboratories has drawn stupendous job to control and maintain the quality standards.

United States of America: [11, 12, 13, 14, 15, 16] In the US, the herbs are classified under dietary supplements by the Dietary Supplement Health and Education Act (DSHEA) of 1994.

Without safety and efficacy profile, the dietary supplements are produced, marketed, and sold, which is a reverse scenario when compared to pharmaceuticals. As per the guidelines stated by the FDA, if the regulators identify a dietary supplement that is not safe for consumption can be detached from the market. The FDA should get evidence of safety and efficacy before the dietary supplement is released into the market by the manufacturer.

There are two categories of herbal drug products; the first category is Over-The-Counter (OTC) and the second category for herbal products that require New Drug Application (NDA) evaluated by CDER of USFDA.

Herbal drug products contain plant materials as ingredients and are labeled as finished herbal products. These products are then marketed after getting NDA approval or ANDA approval or as the counter product. 21 CFR parts 331-358 of FDA regulation states that if an herbal drug product is marketed for a long period for a specific indication, then it is eligible for inclusion in the OTC drug monograph. Under 21 CFR 10.30, a petition must be submitted if the herbal drug product manufacturer intends to amend a monograph to include a new herbal substance.

After the publication of final OTC drug monograph for a specific herbal drug product with regards to a specific indication, any person may market the same product even when it contains that same ingredient as well as usage for the same indication the condition remains that labeling and another active moiety according to the monographs should be submitted by the person. Even in cases where there is no patent protection USFDA will give a market exclusivity of 5 years starting from the date of approval to the drug developer for the new herbal drug product if approved through an NDA.

Under § 314.108(a), a new herbal drug containing several chemical constituents will be eligible to be called a new chemical compound. Unless the second applicant submits a 505(b) (1) application and completes the performance of all the studies necessary for proving the safety and effectiveness of the product, in a case where there is exclusivity granted for a manufacturer of the herbal product, FDA will not approve the application and in most cases will not even review it when the first manufacturer succeeded in the qualification of the product as a new chemical entity as well as usage for a particular indication. If a herbal drug product manufacturer desires to market a product not included in the current OTC drug monograph, rather than requesting the competent regulatory authority to amend a monograph, he should apply for an NDA after proving the product's efficacy and safety.

European Regulations and Guidelines: [17, 18] Under the European Directive 2001/83/EC, marketing authorization for herbal medicinal products is granted based on efficacy, safety, quality, specified tests, and results from experiments. The Directive 2001/83/EC specifies traditional herbal medicine definitions, a listing of community herbal substances, monographs for herbals, and also provisions for a simplified registration procedure.

Under Regulation (EC) No 726/2004 and European Directive 2004/24/EC (2004, Sep), the Committee on Herbal Medicinal Products (HMPC) was established, which is a part of EMA. Most herbal product companies faced a lot of difficulties while fulfilling the requirements of Directive 2001/83/EC for efficacy in particular and European Directive 2004/24/EC simplified their registration procedure.

HMPC Monographs of European Pharmacopoeia provide quality requirements for herbal products and medicinal substances. HMPC guidance documents address various efficacy, safety quality, non-clinical, clinical issues. HMPC has the responsibility to identify priority herbal constituent's/combinations/products, and they should be entered in a monograph.

There are two types of Community monographs: well-established use (marketing authorization) and traditional use (simplified registration). The well-

established use segment refers to efficacy and safety data, while the traditional use segment is prepared based on adequate safety data and probable efficacy. HMPC prepared a community herbal monograph, a requirement for well-established use, marketing authorization, traditional use, and registration of herbal medicines scientifically on the basis of safety and efficacy data of herbal substances. All assessments scientifically done on the existing long-lasting use and experience of herbal products in addition to non-clinical and clinical data in the Community will be documented by HMPC. Most of the herbal medicinal products marketing approval is given by Member states of the European Union separately, but the information regarding the herbal products and their approval is harmonized across the European Union under the directive 2004/24/EC.

On 31 March 2004 European Parliament and Council gave the Traditional Herbal Directive 2004/24/EC which provides a simplified regulatory approval process for herbal medicinal products.

Recent Developments in Regulations of Herbal Medicines across the World: [19, 20, 21, 22] In the 21st century, herbal medicine regulations across the world have shown tremendous changes in regional practices and global implications. By establishing the efficacy profile and regulate the quality and safety by preventing objectionable advertisement to the region-specific cultivation of herbal medicines used by the indigenous people.

In Australia, Herbal Medicine is regulated under the Australian National Medicines Policy. According to the policy, herbal medicines are distinguished into three categories: Registered, Listed or Exempted. Based on the first two categories, the Australian Therapeutic Goods Administration assesses the ingredients and preparations; the manufacturing should be done following the Good Manufacturing Practice codes. The third category deals with the restriction to homeopathic medicines, raw and preliminary materials for conditional use, medicines which are having a definite therapeutic use given by the health care practitioner, and personal use medicines. The labeling of herbal medicine should follow the regulations and recognize the seven active ingredients, and to identify the intended use and dosing instructions as per the standardized constituents provided.

The supervision in the manufacturing and distribution of Herbal medicine is essential in New Zealand. The Medicines Act of 1981 regulates Herbal medicines. The evidence of Quality, safety, and efficacy profile is not required if the Herbal medicine does not include the therapeutic purpose. The Natural Health and Supplementary Products Bill have been passed, which in the future gives the agenda to confirm the quality, safety asserts of OTC products and Health claims. In New Zealand, the changes made to the regulations of herbal medicines are done through the legislative process.

In China, Herbal medicines are regulated under China Food and Drug Administration by the Provision of Drugs Registration; according to provisions, a novel version draft guidelines are currently in progress. For crude drugs and preparations, the herbal medicines should follow the Supplementary Rules to get registered as Traditional Chinese Medicines. Clinical trials are exempted from herbal products that have a long history of use. All the herbal products such as natural products, Chinese medicines, and plant drugs must be following the Traditional Chinese Medicines rules for getting registration.

The Health and Medical Foods (HMF) regulates Herbal medicine in Japan under the “Food with Health Claims” regulations. The Herbal medicine formulation should meet official standards to be registered and licensed as crude compounds and formulations. By the upcoming versions of Pharmacopoeias and non-pharmacopoeial editions, the updation of the official quality standards should be done on time. In 1991 the implementation of Food with Health Claims legislation was passed regarding the unlicensed herbal medicines which are released into the market as health foods, and the recent advances are done in 2015.

Herbal products of Pharmacopoeia grade in Russia are regulated by the laws governing pharmacy grade medications under the “Circulation of Medicines in the Russian Federation”, which was introduced in 2010 September, and its amendment was passed in 2014 (N-429-F3, 11/22/2014). These regulations define procedures and process rules for

licensing of herbal medicines and state registration of herbals, manufacturing methods and logistics, exporting and importing herbals, guidelines for selling and advertisements related to herbals, standardization and QC, R&D, and trials on animals and humans.

In Canada, the Natural and Non-prescription Health Products Directorate (NNHPD) regulates Herbal medicines. In 2004 the Natural Health Products released the current Canadian regulations. The National Health products should have manufacturing and accompanying license and bear a unique 8 digit Natural Product Number to be released into the Canada Market.

Scope for Harmonization: [23, 24] There are defined regulations and monographs for herbal medicinal products in Pharmacopoeias. But there is no uniformity in herbal medicinal product regulations, which is a major concern for the herbal medicinal product manufacturers as they cannot prepare the standardized product for the global market. Also, many countries have defined regulations for herbal medicinal products. As if this is not enough, GMP standards are varying across countries. Pharmacopoeial standards in terms of acceptance criteria, limits for heavy metals, microbial contamination, pesticide limits also vary and this impedes compliance of the herbal medicinal product to the individual country standards.

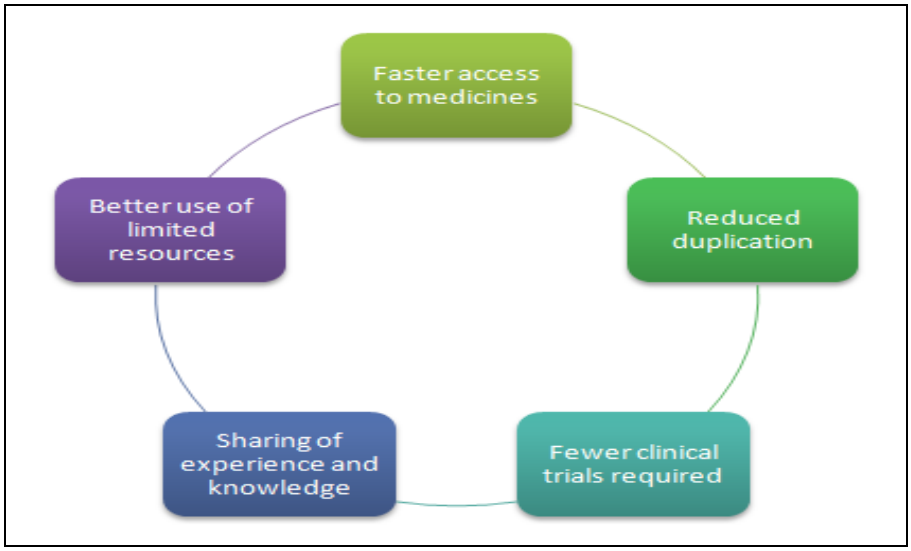

FIG. 1: WHY TO PROMOTE HARMONIZATION?

Harmonization of regulations for herbal medicinal products will lay the path for manufacturing the standardized herbal products with no regulatory hurdles across countries. As it will take time for such harmonization, adherence to the GACP, GMP, GLP, and GCP will ensure a safe and standard product.

Good Agricultural and Collection Procedures (GACP): [25] GACP guidelines give guidance on procedures for cultivation and collection, starting from herbs selection, their identification, soil characteristics, usage of right seeds, techniques to cultivate, surroundings and environment, climatic conditions, factors to be maintained and methods to be used to harvest. Trained personnel who have good knowledge of techniques used in cultivation, usage of pesticides, etc. should only be involved in the collection process. The site where the processes are carried out should be validated for cleanliness, should have proper aeration, equipment that is well oiled and must be in working condition. Machines should be calibrated, and applicators used for pesticides, fertilizers should have less or no contamination. All processes, procedures, labeling, agreements, fumigants, audit results should be documented. Inspection of procedures post-harvesting should be carried out. The specified facilities should be used to process collected herbs, and their storage should be done appropriately.

Details of post Testing should provide information on the usage of solvents, stages of purification, standardization procedures used along with a list of impurities like fumigant and pesticides used, control of microbial contamination. Proper data on stability studies should be provided.

Good Manufacturing Practices (GMP) [26, 27, 28] Batch to batch product consistency and compliance with quality standards to meet regulatory requirements is ensured by implementing GMP standards. Documentation and a proper system for quality assurance will be critical for GMP, which necessitates a facility compliant with US FDA, EU, or WHO GMP regulations. It is mandatory to have an R&D lab that is following GLP requirements as well as being in compliance with the GACP principles. A facility that is satisfying all these conditions would be qualifying for the standardized manufacturing of herbal medicinal products. The process of standardization should be in place right from the seed-related aspects to the final stages of placing on the shelf with properly planned development and validation of methods of analytical techniques.

Process controls accompanying a well-defined process flow in a detailed product development report for herbal products will ensure that quality is built into herbal medicinal products. Processing of herb, herbal product & herbal preparation necessitates a flow chart for manufacture along with a specification for process control and standard testing procedures. Physico-chemical attributes should be included in the active herb specification. Issues related to impurities like contaminants, *i.e.*, microbial contaminants, pesticides, undeclared chemical substances, toxic and heavy metals, fumigants, fertilizers, adulterants, and radioactive substances, should be addressed.

As herbal preparation involves the usage of extraction techniques involving solvents, limits of residual solvents should be specified. Information on stability-related issues of herbal substances, herbal preparations, and the herbal product should be provided. As maintenance of quality-related aspects is partly dependent on container closure system, information in this area is also mandatory.

Good Laboratory Practice (GLP): [29] Developing a quality management system to ensure reproducibility, uniformity, reliability, consistency of the testing parameters in compliance with GLP standards can be ensured by properly planning analytical method development and analytical method validation in accredited laboratories.

Good Clinical Practice (GCP) [30, 31, 32] Under the HATC system (Herbal Anatomical Therapeutic Chemical), herbals are classified based on therapeutic activity and nomenclature for aiding clinical studies and safety. Under the preview of the "Uppsala monitoring center", a collaborating body of WHO will be “HATC”. HATC will publish Guidelines for classifying ATC of Herbals and its index along with their codes.

A pharmacovigilance program was implemented by the Department of AYUSH in 2008 after it considered the rise in acceptance in Ayurveda and the importance of ensuring safety and efficacy while using herbal medicinal products and the attention needed to report adverse effects and their investigation.

Uppsala monitoring (Centre for International Drug Monitoring) handles issues related to herbal pharmacovigilance like adulterants, herbal naming system diversities. Uppsala monitoring Centre, by 2011 compiled 21000 adverse drug reaction reports on herbals across 100 nations in a single database.

For conducting a clinical trial, the Health Authority and Ethical committee give clearance. The pharmacopeias, literature, and monographs are sufficient to know the usage and health conditions in the country. A controlled trial should be carried out in a case where the disease is acute and chronic, and it requires a principal investigator, a protocol that should be in detailed and documented evidence with regards to efficacy and safety of the herbal medicinal product.

Standardization of Herbal Medicine Regulations: [33] Standardization as defined by the American Herbal Product association: "Standardization refers to the body of information and control necessary to produce material of reasonable consistency". The assurance of efficacy, quality, and safety of herbal medicinal products become a critical issue due to the rising commercialization of herbal medicine. The raw material of herbal medicinal products will be prone to variations because of factors like identification of the herbal plant and variations in seasonal cycles, genotypic, chemotypic, and ecotypic, xenobiotic presence, and conditions of storage. This variation can be avoided by reducing inherent

variations in the composition of natural products through the application of QA practices in agriculture and manufacturing procedures. Standardization methods should consider quality aspects like proper identification of the sample, valuation of organoleptic properties, pharmaco-gnostic and Phyto-chemical aspects, materials that are volatile in nature, quantitative attributes like ash values, extraction values, xenobiotic presence, tests for microbial load, toxicity.

TABLE 1: SUMMARY COMPARISON OF HERBAL MEDICINE (HM) DEFINITION AND IT'S REGULATION PATHWAYS IN THE DRUG REGULATORY AUTHORITY SYSTEMS OF THE UK, GERMANY, USA, UNITED ARAB EMIRATES (UAE) AND THE KINGDOM OF BAHRAIN

Regulatory Authority	USA	UK	Germany	UAE	Kingdom of Bahrain
Definitions	Botanical preparations consist of vegetable materials, which include plant materials, algae, macroscopic fungi, or a combination of these materials. Botanical preparations often have unique features, for example, complex mixtures, lack of a distinct active ingredient, and substantial prior human use''	'A product is an herbal medicine if the active ingredients are herbal substances and/or herbal preparations only'' ''The herbal substance being processed can be reduced or powdered, a tincture, an extract, an essential oil, an expressed juice or a processed exudate'' ''A herbal preparation is when herbal substances are put through specific processes which include extraction, distillation, expression, fractionation, purification, concentration and fermentation''	''Herbal products are medicinal products which exclusively contain as active substances, either one or more herbal substances, one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations. Herbal substances are all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form, but sometimes fresh''	Product derived from plant origin is a finished labelled medicinal product that contains as active ingredients aerial or underground parts of plants, or other plant materials or combinations thereof, where in the crude state or as plant preparations intended for prophylactic or therapeutic or other human health benefits'	Herbal product contains as active substances herbal substances or herbal preparations, alone or in combination'' ''A herbal substance is whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh''
Registration pathways	Dietary supplement with DSHEA of 1994 (does not get registered) or Botanical drug with Federal Food, Drug and Cosmetic Act	THR (traditional use) with directive 2004/24/ EC or MA (conventional) with directive 2001/83/EC	THR (traditional use) with directive 2004/24/ EC or MA (conventional) with directive 2001/83/EC	THM (traditional use) or HM with Ministerial decree No. 3276/1997 for registration and re-registration of products derived from natural source	Health product (traditional use) with decree amendments by law No. (20) of 2015 or Medicine with vegetable substance with decree by law No. (18) of 1997
Evidence of quality	Not required for dietary supplements GMP standards and QC tests for botanical drugs	GMP standards and QC tests for THR and MA	GMP standards and QC tests for THR and MA	GMP standards and QC tests for traditional HMs and HMs Declaration of pork free contents Declaration of alcohol content	GMP standards and QC tests for health products and medicines with a vegetable substance Declaration of pork free contents Declaration of alcohol content
Evidence of safety	Not required for dietary supplements unless it is a NDI Toxicological tests for botanical drugs	Bibliographic data for THR Toxicological tests for MA	Bibliographic data for THR Toxicological tests for MA	Bibliographic data for traditional HMs Toxicological studies for HMs	Bibliographic data for health products Toxicological studies for medicines with a vegetable substance
Evidence of efficacy	Not required for dietary supplements Clinical studies for botanical drugs	Long tradition of use for at least 30 years (including 15 years in the EU) for THR	Long tradition of use for at least 30 years (including 15 years in the EU) for THR	Copies of at least two traditional HMs for each herbal ingredient for	Copies of published scientific literature or international

		Clinical studies for MA	Clinical studies for MA	traditional HMs Clinical studies for HMs	monographs for health products Clinical studies for medicines with a vegetable substance
Label requirement	For dietary supplements: must include a disclaimer: ‘‘This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease’’ Must state on the label that it is a dietary supplement	For THR: must include a statement that the product is exclusively based on long-standing use Must include a certification mark (THR)	For THR: must include the words ‘‘traditional medicines’’ and ‘‘traditionally used’’	No requirements	No requirements

CONCLUSION AND RECOMMENDATIONS: Since ancient times, herbal medicine played an important role in maintaining the health of people. Recent researches recognized the Indian traditional medicine like Ayurveda and other systems like Unani and Siddha have a sound scientific background of effectiveness.

Manuals for quality control and guidelines for GACP and GCP have been developed by WHO for medicinal plants and materials. It laid down certain goals for the proper utilization of herbal medicine to improve healthcare and well being of society. The GMP guidelines are set forth by the WHO to assess the quality and safety of herbal products with regard to residue and contaminants. The main objective of WHO is to follow the proper regulations and develop required policies for the delivery of safe products and its use depends on standards, regulations, and procedures which results in the progress of global harmonization that impacts the growth of the herbal market to greater heights. The challenges faced by the herbals in the field of safety, quality, and efficacy can be achieved by framing good practices with the help of harmonized standards and herbal monographs which in the future become a standardized product and enters into the market. Regulations, once harmonized, will make it possible for herbal medicinal product manufacturers to produce a standardized product for the global market.

To overcome issues like irrational use, pharmaco-vigilance, quality control, and standardization, efforts should be taken and to promote herbal medicine, strict implementation of regulations, guidelines, and periodic revisions are necessary.

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