Herbal Product Regulation and Development in India

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ABSTRACT

India's herbal literature pioneered herbalism. In 1945, AYUSH controlled Indian herb production. India offers low-quality items due to globalisation and internet marketing. HMPC created traditional herbal monographs. Prescription, over-the-counter, and self-medication herbal treatments are available. Ayurveda dates to 1000 BC's Atharvaveda. India's Drug and Cosmetic Act (D and C) 1940 and Rules 1945 regulate herbal medications. Years have been spent questioning AYUSH products' quality, effectiveness, and safety. Schedule "T" implemented GMP in 2016. Herbal drugs are tested on humans following animal testing, per GCP criteria. Herbal remedies and therapeutic plants must be carefully evaluated for Allopathy. This excludes Ayurveda, Unani, and Siddha clinical trial recommendations. Safety, quality, and efficacy are significant challenges in commercialised herbal medicine substitutes, adulterants, and metals contaminate Indian herbal medicine. Due to their lengthy history, Ayurveda, Siddha, and Unani are safe in India. The 1940 Drugs and Cosmetics Act does not mandate safety and efficacy studies. Before pharmaceutical creation, clinical trials, and dossier submission, most responses seek scientific counsel. Quality impacts herbal drug safety and efficacy. Herbal drug monitoring is difficult, especially combinations. In developing countries like India, population expansion threatens food and medicine supplies. Lack of global standardisation and quality uniformity hinders medicinal plant commerce. Indian Ayurvedic, Siddha, Unani, and homoeopathic systems use herbal medicines. World Health Organization has emphasised adopting new procedures to assure herb quality.

Keywords: Herbal Drugs, Ayurveda, Siddha, Unani, World Health Organization (WHO)

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INTRODUCTION

Modern medicine is well-developed in much of the world, yet people still want herbal remedies. Several plants have been deemed beneficial. Ayurveda lists medicinal herbs. Many firms make Ayurveda-based supplements. Herbal products were formerly considered safe, but we now know differently. We discovered no usage instructions for herbal products offered in India. Allopathic medicine is different. A pharmaceutical company invests much in bioavailability, toxicity, safety, clinical data, etc. to verify its efficacy. Most herbal products fail because they lack this. We can assess how strict governments are regarding human safety by examining herbal product laws across the world.

Herbal medications are categorised by their active metabolites. First, rudimentary drugs. Plant-derived active components Herbal extracts are second. These pure compounds and pharmacologically stronger active. Third, natural medicines with acute Available chronic animal toxicity studies.

India's herbal literature pioneered herbal treatment. India's natural drug monitoring is lacking. India sells global herbs. Globalization and online marketing make India offer low-quality goods. Pharmacovigilance does not examine herbal product interactions. AYUSH controlled Indian herbal product production in 1945. Unfinished. Worldwide treaties like CITES control the international commerce of herbal medications (CITES).[1]

Herbal substances

All unprocessed forms of plants, plant parts, algae, fungus, and lichen in their natural,

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mostly dried, but occasionally fresh, state, including entire, fragmented, or cut specimens. Some exudates that have not been processed in any particular way are also regarded to be compounds derived from herbs. The component of the plant that is utilised and its botanical name are what are used to define herbal compounds exactly. This is done using the binomial system (genus, species, variety, and author).[2]

EU standardises licencing and information for herbal medicines. Companies must verify a product's quality, safety, and patient information before registering it in the UK (THRS). Small traditional claims. Regardless of legislation, herbal medicine quality must be maintained. HMPC developed herbal monographs for traditional and well-established usage.

WHO defines four groups of herbal medicines:

- Indigenous or Local herbal medicines: Locals have long utilised this type of natural medications for therapy, composition, and dosing.
- Herbal medicine in systems: This category of drugs has been used for a long time, is well-documented and is well acknowledged. Example, Ayurveda, Unani, and Siddha.
- Modified or changed herbal medicines: In this category, herbal remedies are modified in structure, shape, dosage, administration, preparation, medicinal indications, and constituents. Herbal medications must meet National Regulatory criteria for safety and efficacy.
- Imported herbal drugs (raw materials and products): Imported herbal medicines must be registered and sold. The drug's safety and efficacy must meet the importing country's standards for herbal medicines.[3]

Herbal medications can be sold in three categories:

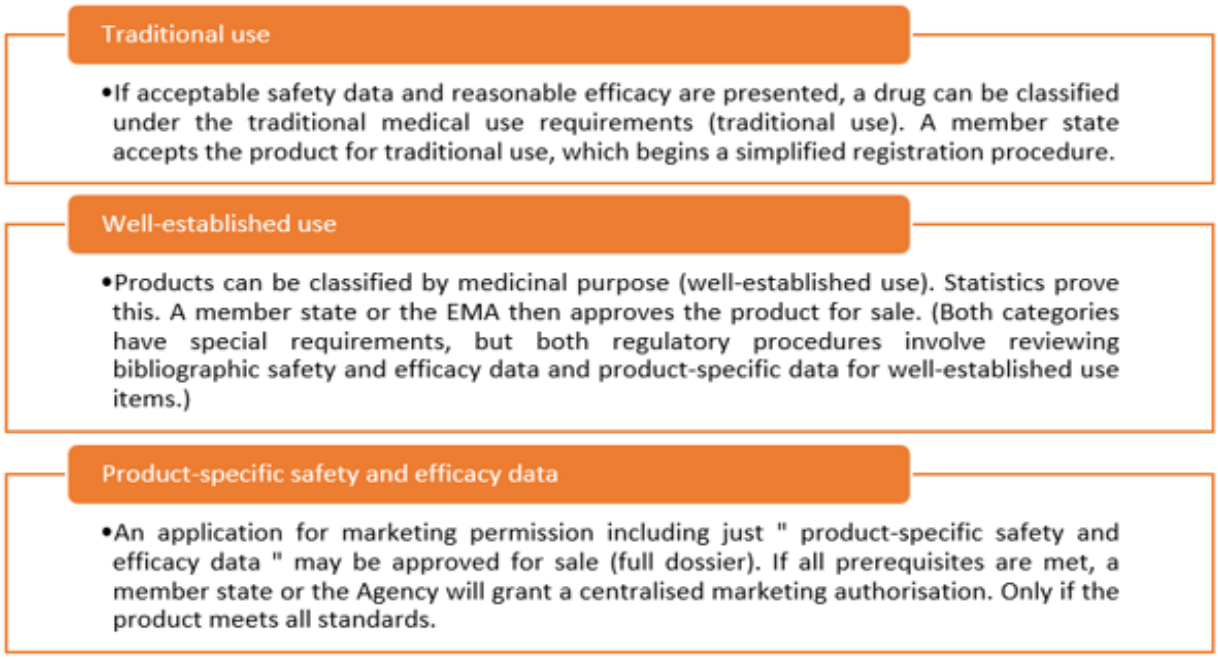

Figure 1: Categories of Herbal Medicines

Historical Background

Humans have utilised natural products from plants as food and medicine, notably plant parts or complete plants to heal and prevent disease. It's impossible to quantify when humanity started utilising plants as medicine, but ancient literature and other sources indicate its beginning. A 5000-year-old Sumerian clay slab from Nagpur has the oldest written record of therapeutic plant usage. It had 12 drug production formulas and over 250 plants, including poppy, henbane, and mandrake. Indian holy books Vedas mention treatment with herbs abundant in the land.

Each nation has a different document on using plants and herbs to heal and cure sickness. Ayurveda is India's 5000-year-old medical system. Ayurveda is from 1000 BC's Atharvaveda. The earliest Ayurvedic text book was written in Sanskrit. Ancient Ayurveda promoted health, not sickness. Charaka Samhita

(1000 BC) and Sushruta Samhita are herbal texts (100 AD). Ayurveda text medica describes 1500 plants and 10,000 formulas. Madhav Nidan describes diagnostic traits and symptoms of over 5000 illnesses and disorders (800 AD).[4]

Regulatory Status

- Member states were questioned about herbal medicines' regulatory statuses. The survey form described seven regulatory classes for herbal medications. Prescription, over-the-counter, self-medication, herbal medicines as a separate regulatory category, dietary supplements, health foods, functional foods, and another status.
- As each state might pick more than one group, the overall number of replies surpasses the number of responses. Over-the-counter medication was chosen 97 times. Next most popular were prescription drugs, nutritional supplements, and self-medication. 23 nations do not regulate herbal medications.
- 13 nations described other legislative categories. Health goods, cosmetics, medicinal products, herbal treatments, supporting medications, homoeopathic, bioactive, and probiotic agents, and complementary products are also regulated.[5]

INDIA

- The Drug and Cosmetic Act (D and C) 1940 and Rules 1945 regulate this burgeoning herbal business in India. AYUSH regulates herbal product manufacturers. Sections C and D cover formulation composition, licencing, labelling, manufacture, packing, quality, and export.
- Schedule "T" implemented GMP in 2016. (GMP). In India, herbal medications are regulated by the Drug and Cosmetic Act (D and C) 1940 and Rules 1945, Chapter IV-A. 33C-33O have 18 parts.
- It strives to ensure scientifically and ethically sound investigations and well-documented clinical aspects of ASU medications. Standards protect human subjects' rights and authenticate ASU clinical trial data.
- Under DCA 1940 and Rules 1945, AYUSH controls herbal products. Herbal drugs are licenced. Schedule T (Chapter IV-A) gives herbal companies GMP. AYUSH develops healthcare. 33C-33O cover manufacturing, certification, sales, licence, GMP certificate, and penalties. Products must carry production and expiry dates since 2017. India takes 3 months to approve drug trials. Pharmacopoeias and guidelines control drug quality. DCA's first schedule lists herbal medication registration texts.[3]

Rules, Regulation & Governing Body

The Drug and Cosmetic Act was revised to reflect India's recognition of ISM in 1959.First official EWG for ISM was formed in 1962. Act 13 of 1964 created a segment for Ayurveda, Siddha, and Unani. 1983, 1987, 1994, and 2002 saw statutory changes. DCA Rules 1945 gave criteria for ISM pharmacological analysis in 2006 and 2008.

The CCIM was founded in 1970 and created ISM's curriculum and syllabus. CCIM accepted Tibetan medicine in 2012. The ISM & H Department was created in 1995 to develop ISM. In 2003 to 2014, a separate AYUSH department was formed, which in 2009 introduced a certification process for AYUSH herbal pharmaceuticals. AYUSH products' quality, efficacy, and safety have been questioned for years. To address these difficulties, QCI and AYUSH created a voluntary approval process.[6]

Drug Development Process of Herbal Medicines

The following are components of the Drug Development Procedure for herbal medicines in general:

- The first step is to make a synthetic version and isolate the bioactive component.
- Second, Analysis of effectiveness and security.
- Finally, if a novel drug is being developed, the regulatory process must approve the therapeutic agent pharmacological testing in humans, or clinical trials, lastly.

Drug standardisation comes first, then studies on the drug's biological activity and safety, then preclinical testing, etc. In the right areas, you'll find an appendix with the standardisation process for various formulas.

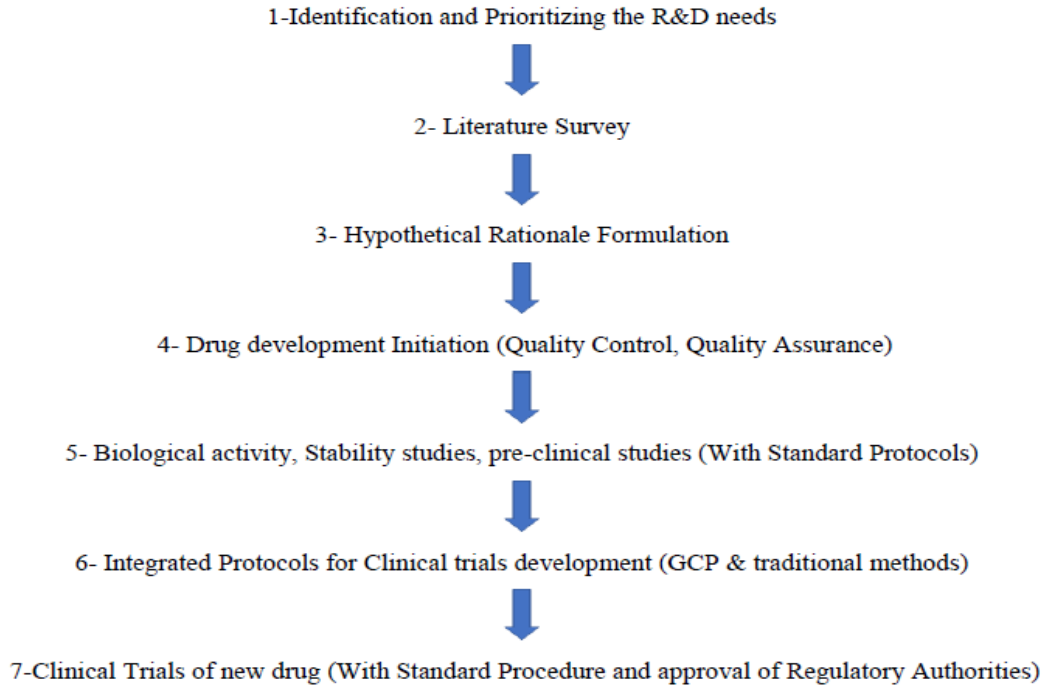

Figure 2: Drug Development Process of Herbal Medicines[3]

CLINICAL TRIALS OF HERBAL MEDICINES

Herbal medications are tested on humans after animal testing, per GCP guidelines. DCGI regulations require herbal medicines and medicinal plants to be scientifically evaluated for use in the Allopathic System and Allopathic hospitals. This doesn't apply to Ayurveda, Unani, or Siddha clinical trial recommendations for their own facilities.

Stages of Clinical Trial

• Phase I studies

Herbal medications don't need phase 1 studies since they may be safely supplied to few clinical participants in phase II trials. Phase I takes months.

• Phase II studies

This phase tests dosage in sick patients (100-300). This step determines dose ranges and dose-response relationships for designing large clinical trials. This step checks tolerance. Clinical safety factors should guide literature reviews and procedural recommendations. Phase II studies encompass hundreds of patients over months to years.

• Phase III studies

This phase extends phase 2's safety and efficacy research. This phase includes 1,000 to 3,000 hospital or clinic patients. Herbal medication adverse effects are monitored. This trial confirms the drug's safety and efficacy. This time takes 3 years.

Randomized phase 2 & 3 studies compare treatments in two groups. One group gets experimental treatment, another a placebo. Patients and researchers don't know who gets the experimental treatment in phase studies.[7]

Guidelines for Good Clinical Practice for Herbal Drugs And Products in Conducting Clinical Trials in India

- Herbal drugs and plants should be declared in a Traditional System of Medicines and made according to Good Manufacturing Practices. Phase 1 trials are unimportant. To be examined, compounds must be in Indian System of Medicines books.
- Animal toxicity must be reduced. Until a study reveals toxicity or when to use herbal drugs, phase 2 clinical trials do not need toxicity investigations. In all circumstances, two animal species must undergo a 4- to 6-week toxicity test.
- Standardizing herbal medicine clinical trials ensures consistent results. Clinical trials on plant therapies require informed permission, participants, inducements, patient information, withdrawal, and research involving children or people with decreased autonomy. These experiments need scientific and ethical approval.

- Ayurvedic, Siddha, or Unani doctors must be co-investigators. Untrained in alternative medicine, an allopathic doctor should not perform clinical investigations on the herb. Clinical exams should include a representative from each system.[8]

GCP Guidelines contains

- Introduction
- Definitions
- Pre-requisites for the study
- Protocol
- Ethical and safety consideration
- Informed consent process
- Compensation for participation
- Responsibilities of sponsor, monitor and investigator
- Data handling
- Record keeping
- Quality assurance
- Statistics
- Special concerns
- Appendix I: guideline for evaluation of ayurvedic, unani and siddha medicine
- Appendix II: ethical issues
- Appendix III: investigator's brochure
- Appendix IV: essential document. [8]

Standardization and Commercialization

As herbal medicine has become commercialised, safety, quality, and efficacy have become key issues. The herbal raw material varies owing to numerous aspects, including the identification of the plants and seasonal change (which affects collecting time), ecotypic, genotypic, and chemotypic variations, drying and storage conditions, and the presence of xenobiotics. Standardization as defined by American Herbal Product association: "Standardization refers to the body of information and control necessary to product material of reasonable consistency. Agricultural and manufacturing quality assurance approaches minimise natural product composition volatility. Standardization procedures should address sample identification, organoleptic, pharmacognostic, volatile, quantitative (ash, extractive), phytochemical, xenobiotic, microbial load, toxicity, and biological activity evaluations. It affects herbal medicine activity. Fingerprint profiles serve as a reference to the medicine's phytochemical profile to assure quality, and marker compound quantity is another quality metric. Phytochemical standardisation encompasses herbal medication ingredients.[9]

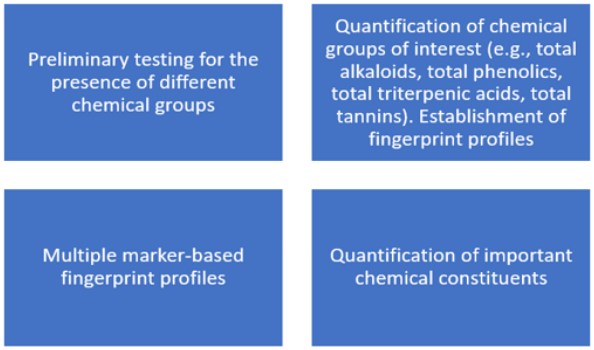

Figure 3: Various Phytochemical evaluation for standardization purpose

Herbal remedies are common in India. Most traditional Indian practitioners create and sell their own concoctions, making market size unknowable. Large companies sell $300 million a year, compared to $2.5 billion for modern drugs. General practitioners are inexperienced with Ayurvedic medicines, even if some are prescribed. If an Ayurvedic product's efficacy is proven, they'll test it. Coughs, colds, diarrhoea, and stomachaches are self-medicated. Over-the-counter pharmacies sell Ayurvedic patent medicines. These are a big part of branded traditional Indian items. Ayurveda requires evidence from modern medicine to be credible and recognised. Innovative research on traditional medicine's safety and efficacy might boost its use.

Standardization of herbal formulation

Good Manufacturing Practices (GMP) are needed to standardise herbal formulations (WHO guideline, 1996). Herbal formulations must be studied for pharmacodynamics, pharmacokinetics, dose, stability, self-life, toxicity, and chemical profiling. Heavy metal contamination and Good Agricultural Practices (GAP) in herbal medication standardisation are crucial.

Issues with the standardization of raw materials

Indian herbalists worry about raw material standardisation when quality is questioned. Ayurvedic treatments have 600 plant, 52 mineral, and 50 animal ingredients, according to AYUSH. Taint herb cultivation, collection, and processing. Over 50% of organisations have trouble sourcing and confirming raw materials,

according to study. 54 firms (36%) consider raw material adulteration common. Indian herbal medicine has substitutes, adulterants, and metal contamination. Raw material gathering and production yield heavy metals. Preharvest, postharvest, and storage are risks for microbial and mycotoxin contamination. Herbal medications hinder quality control. Natural products analysts employ compounds as identifiers and quality indicators. Herbs are identified by taxonomy, chemistry, genetics, and proteomics. Industrialized nations test raw materials and active compounds. India just agreed. Indian GMP doesn't use markers. 44% of firms use chemical markers to analyse their formulations. Marker-based analysis costs money. Most Indian SMEs cannot afford R&D. 10% of companies have R&D. Standardizing raw components and mixtures uses physical/ chemical/physiochemical approaches. Marker-based research is limited since not all therapeutic herbs/plants have standards. India and outside lack third-party labs to assess Indian components.

Steps to be taken to improve the existing efforts of standardization

1. Control on quality of raw materials

Herbal drug quality depends on raw materials. Most raw resources are wild-sourced, with minimal cultivation or collecting. Controlled cultivation can improve quality. Good farming and harvesting yield high-quality raw materials. Good Agricultural and Collection Practice for Medicinal Plants (GACP) has been published in Japan and China. WHO created GACP for medicinal plant cultivation and collecting.

2. Research for developing quality control methods

Herbal drugs, especially combinations, have poor quality control. Modern standardisation needs study. This industry requires more attention despite attempts. Ayurveda requires additional plant monographs. We will utilise stricter standards and better equipment. Metabolomics and marker molecule research must be prioritised.

3. Clinical trial

In third-world countries like India, working groups and experts lack coordination and effort to translate and utilise clinical trial data. Most modern doctors and researchers believe in extensive screening and clinical trials, whereas traditional medicine specialists are sure their drugs are 100% effective and deem clinical studies redundant. In China, traditional medicine colleges base their treatments on logic, not science. Clinical trials need clinical pharmacists, pharmacologists, and apothecaries. [10]

Differing regulatory requirements

- Differing regulatory requirements and delays in application filing and assessment were a major worry for herbal medicine manufacturers.
- To comprehend the disparities in approval procedures and submission requirements, India, the U.S., and European nations' drug registration requirements were compared.
- Ayurveda, Siddha, and Unani (ASU) are regarded safe in India due to their long history of use. The 1940 Drugs and Cosmetics Act requires no safety and effectiveness investigations for marketing authorisation (DCA).
- SFDA regulates manufacturing and marketing approvals. Most Indian herbal therapeutic medicines are sold as dietary supplements in the U.S.
- Marketing authorisation does not require safety or efficacy evidence. Manufacturers must prove the safety of their products, thus no sickness or disorder claims are allowed.
- Dietary supplement manufacturers don't need FDA permission to produce or sell their goods. After a dietary supplement hits the market, the FDA must take action.
- Maximum export to the US (survey result) can be associated to reduced dietary supplement rules. Because doing so requires no scientific evidence, Indian manufacturers prefer to advertise their items as dietary supplements without health claims.[11]

Lack of regulatory guidelines

Insufficient regulatory standards for production are a major cause of herbal medicine quality difficulties, according to a survey. 60% favoured herbal medicine quality control. ASU and other traditional treatments have been promoted for preclinical safety research, however standardising herbal preparation and marker-based active component identification is necessary. Herbal medicine production and preservation require GACP. India's National

Medicinal Plants Board outlined agricultural and field collection standards in 2009. According to our findings, most manufacturers and sellers don't know about these constraints. Due of farmer education and operating costs, many organisations find these plans unrealistic. Great medicines need standardised raw ingredients and extracts. Each state will have supply centres. Respondents wanted enhanced raw material quality control.

Indian drugs are mostly over-the-counter. OTC herbal remedies are driven by advertising and client demand, whereas doctors prescribe. Half of survey companies undertake pharmaceutical safety research, and 12% conduct clinical trials. India lacks natural drug trial guidelines. 2008's 4th Amendment Rule regulates ASU drug testing (Rule 170). New guidelines classify ASU medicines by required clinical studies. ASU therapies and plant-based medications don't need clinical evidence. Hydroalcoholic extracts, ASU, and Indian ethno medicine need testing. Ayurveda employs powders, liquids, and decoctions. Unusual hydroalcoholic extracts. Ayurvedic formulae can't contain hydroalcoholic extracts. New aqueous-extract indications require clinical investigation.

Implementing and regulating DCA is another Indian herbal business issue. Only 107 firms were GMP certified, despite it being mandatory since 2006 according DCA Schedule T. The SFDA reads the DCA differently, therefore an unapproved medicine or formulation is allowed. State registration timelines vary. Similar methods, dates, and criteria will eliminate state licencing authority anomalies and establish a unified system nationally. Most respondents need scientific advice before medication development, clinical trials, and dossier submission.

According to our interview research, 90% of herbal pharmaceutical facilities are tiny. Our survey shows companies want standardised raw materials. GACPs assist growers and collectors produce high-quality material. Organic food is healthy. Some drugs are grown. Government supports SMEs. Most small businesses don't know about subsidies. Promote government aid and facilities.[12]

Methodology of Herbal drug research

• Health Benefit

An effect of a nutraceutical that promotes a healthy lifestyle, protects against or lessens the probability of developing an illness, involves disease management, or protects against or lessens the severity of an existing disease.

• Health Claim

Food labels may include health claims. They relate a vitamin or dietary component to a condition or illness. These are for traditional meals and supplements.

• Safety:

It is a treatment's unwanted effects. Herbal medications are generally considered safe. Case studies show significant adverse effects and medication interactions may occur. Numerous accounts detail the herb's side effects and interactions. Several plants are dangerous, and herbal compositions can be contaminated, faked, or misinterreted, increasing adverse effects and difficulties.[13]

Challenges Involved:

• Challenges Associated to The Regulatory Status of Herbal Medicines

A dietary supplement is an ingested "dietary ingredient." These may contain vitamins, minerals, herbs, or botanicals. DSHEA doesn't require toxicity testing if a herb was on the market before 1994. FDA must prove herbal medication or "dietary component" is harmful. In many nations, regulatory organisations, safety training, or pharmacovigilance centres don't share herbal medicine information.

• Challenges Associated to the Assessment of Safety and Efficacy:

Herbal medicine law, theory, practise, standards, and methodologies are complex. A single herbal cure or medicinal plant may have hundreds of natural compounds. A combination product may have more. Multi-plant herbal medicines may have multiple active ingredients.

• Challenges Associated to Quality Control of Herbal Medicines

Herbal medication quality affects safety and efficacy. The quality of raw materials depends on intrinsic (genetic) and extrinsic variables such as environmental conditions, great farming, and optimal plant selection and culture for medicinal plants. Many variables make herbal medication quality monitoring difficult. GMP demands accurate identification, storage,

and cleansing of medicinal plants and components. Monitoring herbal medications, especially mixes, is challenging. Herbal products offer stricter quality control than conventional drugs. WHO encourages quality control systems such as National Quality Standards and Guidelines for Herbs, GMP, labelling, and manufacturing licencing programmes to ensure the effectiveness and safety of herbal treatments.

• Challenges in Medicinal Plants Sector:

Population growth in developing nations like India is a worry for fulfilling daily food and medicinal demands, as the economy and livelihood of communities rely on forest products. This phenomenon causes forest and forest product erosion, making it difficult to satisfy requirements and protect natural resources. As new species are added to Materia Medica, their purity and authentic identification do not keep pace. Market pricing for medicinal plant products give only a limited view of the market's earnings, supply, and demand. Due to price, quality, and quantity, collectors and merchants have trouble finding favourable marketplaces. Inadequate knowledge and inaccurate information about items, markets, and pricing by collectors and lack of standardisation and consistency in quality for worldwide selling cause challenges in medicinal plant trading.[14]

Future Aspects

In many developed countries, research institutes, universities, pharmaceutical labs, and hospitals do intensive study on therapeutic plants. This research is two-fold. First, therapeutic plants' active compounds are studied. Second, fundamental research focuses on finding novel therapeutic plants and pharmaceuticals in remote corners of the planet.

Ayurvedic, Unani, and Siddha drugs must be tested scientifically. CSIR, New Delhi, has certified 350 formulations for varied activities. This movement is welcome since it combines traditional and modern health practises. WHO has emphasised adopting new procedures to assure herb quality. Several countries maintain herbal pharmacopoeias with monographs. The Indian Ayurvedic Pharmacopoeia specifies quality standards for 80 herbal medications.[15]

CONCLUSION

Indian Ayurvedic, Siddha, Unani, and homoeopathic systems use herbal medicines. The Department of AYUSH, ICMR, and CSIR collaborate on research and development of innovative pharmaceuticals and safe and effective AYUSH remedies for specific illnesses. The AYUSH department has begun implementing a certification system for AYUSH pharmaceutical items. The registration procedure in India is not well controlled, despite the country's efforts to set guidelines for the clinical testing of herbal medicines.

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Conflict of interests

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Ethical approval

Since this work does not involve any animal studies it does not require Ethical approval

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