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Challenges in Quality Control of Herbal Pharmaceuticals: Standardization, Analytical Methodologies, and Regulatory Frameworks

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ABSTRACT

Herbal pharmaceuticals have long been utilized as natural therapeutic agents and are increasingly recognized for their potential in modern healthcare. However, the advancement and global acceptance of these products are significantly hindered by persistent challenges in quality control, standardization, and regulatory compliance. This review critically examines the core issues impeding the development and validation of herbal medicines. The variability in phytochemical profiles attributed to genetic diversity, environmental factors, and post-harvest conditions complicates efforts to ensure consistency and reproducibility in product quality. Additionally, widespread adulteration and the lack of well-defined pharmacokinetic and clinical data limit their credibility in evidence-based medicine.

The application of modern analytical techniques, including chromatography, spectroscopy, and DNA-based authentication, has enhanced the ability to identify and quantify bioactive constituents. However, their integration into routine quality control practices remains inconsistent. Regulatory disparities across countries further compound these challenges, creating barriers to international harmonization and market approval. Moreover, clinical validation of herbal products is complicated by methodological issues, such as the design of placebo-controlled trials and ethical considerations related to traditional knowledge systems.

To address these challenges, a multidisciplinary strategy is required one that bridges traditional medicinal systems with advancements in pharmacognosy, molecular biology, and regulatory science. Strengthening global regulatory frameworks, implementing rigorous quality standards, and encouraging comprehensive clinical research are essential steps toward ensuring the safety, efficacy, and wider acceptance of herbal pharmaceuticals in modern medicine.

INTRODUCTION

For decades, traditional healthcare systems throughout the world have relied heavily on herbal medications made from therapeutic plants. Due to their perceived safety, holistic therapeutic potential, and rising consumer desire for alternative and complementary medicine, these natural products have seen a global upsurge of interest in recent decades [1, 2]. Despite this increased focus, ongoing issues with regulatory monitoring, standardization, and quality control continue to limit the use of herbal medications in mainstream healthcare [3]. The complicated and varied character of herbal remedies, which frequently contain several bioactive substances, makes it difficult to guarantee constant efficacy, safety, and quality. In contrast to synthetic medications with clearly established structures and pharmacokinetics,

herbal treatments depend on a variety of variables, such as the diversity of plant species, farming methods, harvesting circumstances, processing techniques, and storage settings [4,5]. Quality assurance is a crucial concern since these factors influence variations in the phytochemical makeup of herbal preparation [6]. Furthermore, the ability to authenticate raw materials and validate final products is hampered by the absence of widely recognized analytical standards and the uneven application of contemporary techniques like nuclear magnetic resonance (NMR), gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), and DNA barcoding [7,8]. These issues are made worse by national regulatory disparities, which result in disjointed monitoring, inconsistent safety requirements, and barriers to international market entry [9, 10].

The many problems preventing the quality control of herbal medications are examined critically in this study, with particular attention paid to the deficiencies in regulatory frameworks, analytical techniques, and standardization procedures. It also emphasizes the necessity of unified worldwide approaches that combine scientific advancement with traditional knowledge to

guarantee the safe and dependable application of herbal remedies in contemporary therapeutic contexts.

Advancements in herbal medicine: Integrating traditional knowledge with modern scientific approaches

Improvements in herbal medicine: The Interweaving of Traditional, Longstanding Knowledge with Current Scientific Practice Ayurveda, Unani, Traditional Chinese Medicine (TCM), homeopathy, and naturopathy represent plant-centered medical systems that have existed for centuries. These traditional practices were, however, often disregarded and in some cases, made illegal during colonialism, as these practices were deemed obsolete and unscientific. By the early 19th-century chemical analysis had become an important new scientific technique that enabled researchers to separate and use active bio-chemicals from plants with efficacy [11]. Once it was established that chemists could replicate botanicals and other natural substances, it became possible to produce new pharmacological medications. Interestingly, approximately 25% of all allopathic prescription medications contain at least one plant-based active ingredient [12]. Recent studies have shown that herbal medicines can provide comparable efficacy and a somewhat safer delivery mechanism than conventional medications [13].In particular, for example, plants produce antimicrobial peptides to defend against microbial infections. Antimicrobial peptides exhibit strong potential as therapeutic pharmaceutical agents compared to conventional medicine. Antimicrobial peptides selectively target prokaryotic cells, which leads to diminished mechanisms of microbial resistance [14]. Recently, growth in the science of vaccine development in response to the SARS-CoV2 pandemic utilizing self-assembling peptide nanofibers indicate a potentially strong vaccine platform [15].

The area of herbal medicine research has also greatly leveraged advancements in genomics. Genomics plays a major role in understanding gene clusters and gene duplication events associated with specialized metabolism, highlighting gene-metabolite discovery in medicinal plants.

Comprehensive genome sequencing, annotation, and assembly are fundamental for elucidating gene functions associated with secondary metabolite biosynthesis, including terpenoids, alkaloids (e.g. flavonoids, iso-flavonoids), and phenolic compounds. However, to date, only a few well-assembled herbal genomes have been published. Furthermore, genomic studies of medicinal plants can integrate genomic information with **proteomic, transcriptomic, and metabolomic** datasets, enhancing our understanding of secondary metabolite biosynthesis in medicinal plants (16). This intersection point between traditional herbal medicine and modern-day science provides many new opportunities for drug discovery and therapeutics. As research in genomics and molecular biology expands, we will uncover the full potential of plant-derived medicines. Herbal products, either single or multiple forms of an herbal product, are widely used within traditional medicine practice.

The majority of indigenous formulations- including Ayurveda's well-known Chyavanprash- incorporates multiple plant species (typically greater than 5 individual herbs), which can include upwards of 40 individual botanicals. Some traditional delivery systems also utilize animal- and mineral components. They can come in many forms: as raw, powdered plant form, or plant extract, which have been extracted using different extraction methods (hot or cold) and solvents that could be water, alcohol, ether, or based on the polarity of the target therapeutic bioactive constituents, the excitants. This is then prepared under ultra-low temperatures to produce a concentrate in a liquid or paste form, or dried to a powdered state using lyophilisation.

Herbal formulations also contain a very complex spectrum of secondary metabolites, including alkaloids, terpenes, sterols, flavonoids, phenolic, glycosides, saponins, tannins, and other bioactive ingredients. Due to this complex mixture of components, identifying what compound is responsible for a specific therapeutic setting is challenging. Additionally, various processes, including heating and boiling, used during formulation and storing food may altered or denatured the pharmacological effectiveness of the active therapeutic constituents. Environmental parameters, such as precipitation, sunlight, temperature, altitude, soil composition, relative humidity, and more can cause toxicity due to chemical changes in the raw plant material, leading to significant variations from batch to batch of consumer product. Other important variables such as infestation of pests or competition in habitat, density of species, their conditions of sowing and harvesting, and genetic aspects of components also detrain the safety and variability of herbal formulations. Understanding these complicated challenges of plant variability is essential to ensure quality, safety, and therapeutic efficacy in herbal products for use in modern day [17].

Difficulties in formulating standardized herbal products and drug forms

The effective formulation and use of herbal medicines rely on three fundamental principles:

1. A standardized, regulatory system and uniform quality control systems need to be put in place for the herbal product for which the study is conducted or the clinical trial is being conducted.
2. A substantial amount of scientific information supporting the clinical efficacy of the product must come from clinical studies.
3. Toxicity, without the deliberate incorporation of a toxin(s), must be documented through a well-designed clinical study that will secure the safety of humans. In order to provide greater reliability and global utilization of herbal medicine, especially in established countries, rigorous methodological requirements should be in place for quality control and standardization.

Each supply chain has quality requirements that must be met, which are:

(i) Meeting pharmacopoeia requirements, which include loss on drying, ash content, and extractives, that are unique to each medicinal plant and specific to the regulatory context of each country.

(ii) Authentication of herbal substances and/or active ingredients through botanical characterization and distinct analytical methods, such as phytochemical characterization through High-Performance Thin-Layer Chromatography (HPTLC) and/or High-Performance Liquid Chromatography (HPLC) fingerprinting.(iii) Adherence to acceptable levels of heavy metals, aflatoxins, microbial load and levels of specific pathogens.

(iii) Compliance with acceptable levels for heavy metals, aflatoxins, microbial impurities, and certain pathogenic organisms.

(iv)The final formulation should be free from toxic plant chemicals such as cyanogenic and cardiac glycoside compounds.

(v) The safety of the herbal formulation should be determined through preclinical toxicology studies in animal models. In India, the regulatory framework and standardization of herbal drugs falls under the **Drugs and Cosmetics Act (1940)** in ministries of Health and Family Welfare and the **Indian Council of Medical Research (ICMR), New Delhi**. Following these regulations will promote safety, quality of herbal medicine, and their legitimacy in international markets [18].

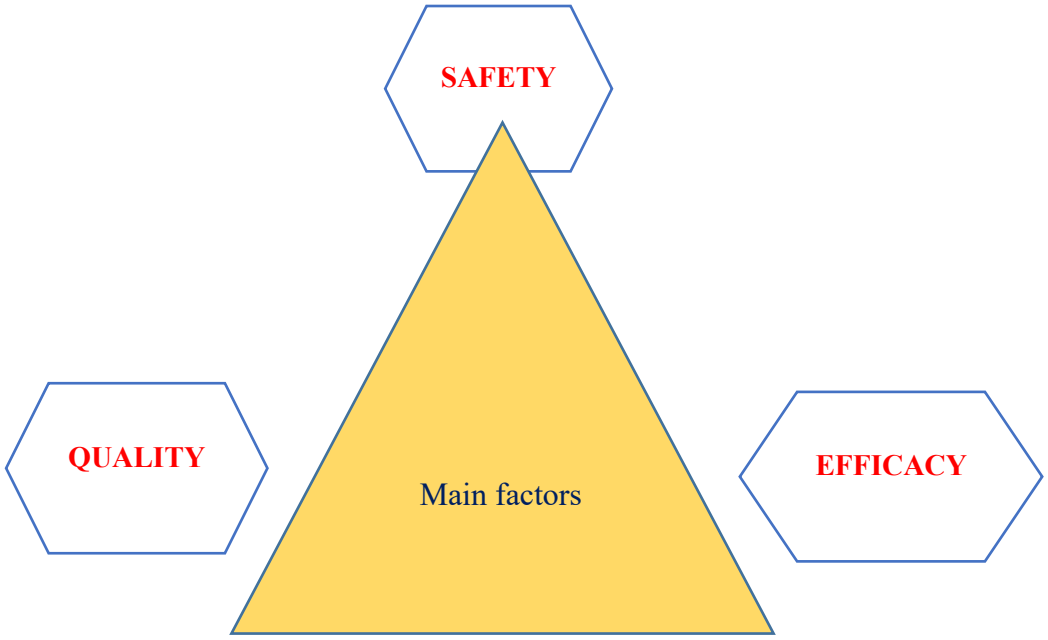

Fig 1. Main factors to be considered in the herbal medicine

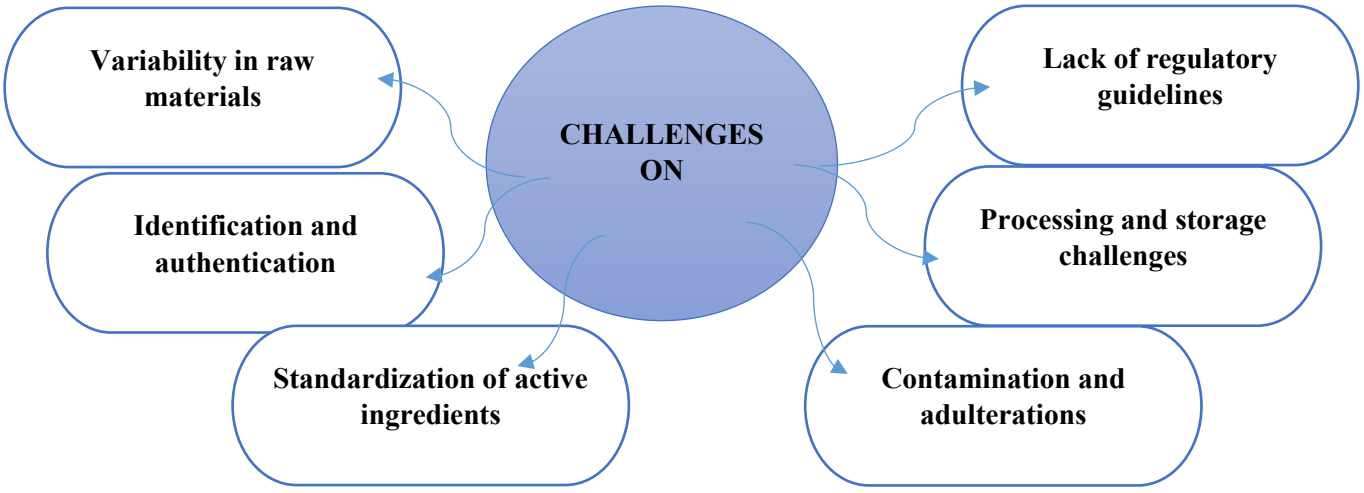

Fig 2. Challenges in the quality control of herbal medicine

Variation in raw materials and collection issues

The physiologically active compounds found in plant sources, which are divided into primary and secondary metabolites, are primarily responsible for their therapeutic effects. Abiotic and biotic variables, such as the plant's genetic composition, the climate of its natural habitat, seasonal variations, and growth and development, all impact the synthesis of these phytochemicals, particularly secondary metabolites [19, 20]. Traditional Indian medical systems, or AYUSH, outline established guidelines for the collecting of medicinal plants. These guidelines specify several elements, including species identification, geographic location, ecological characteristics, seasonality, and, in some situations, the optimal development stage for harvest [21].

There is currently a good deal of evidence in the scientific literature showing variations in these variables significantly influence the presence and concentration of secondary metabolites in medicinal plants [22, 23]. Establishing reference standards and differentiating quality for the countless species utilized as medicinal plants becomes crucial when one considers the variety that affects secondary metabolites in the raw materials. This can include combining contemporary scientific methods with traditional knowledge systems, like traditional books on Indian medicines [24].

In light of this variability, it is essential to create reference standards and define quality metrics for medicinal plant species through a combination of traditional Indian medicinal literature and contemporary science. The capabilities of sophisticated analytical equipment will allow for even more rigorous culling, supporting a stronger and more effective standardization strategy that better ensures quality and efficacy for herbal medicines [25].

• The chemical make-up of medicinal plants can be influenced by environmental factors which can include, but are not limited to, soil make-up, climate, altitude, temperature, and variations between seasonal growth and harvest.

• Plant genetics, choice of species, and geographic location will also play a role in batch-to-batch variability.

• Quality of raw materials will also be influenced by harvesting time, maturity stage and post-harvest handling processes.

Identification and authentication

• Accurate identification of plant species is important to minimize the potential for adulteration and replacement with inferior herbs.

• Identification often requires macroscopic and microscopic observation, as well as chromatographic and spectroscopic techniques, to verify identity.
• Identification may be challenging due to considerable morphological similarities between plant species, and this can compromise therapeutic effectiveness.

Medicinal plants have a variety of therapeutic effects and may contain specific therapeutically active compounds present in different parts of the plant. Some plant organs may have therapeutic value, while others may have toxicity depending on differences in the active components. Misidentification or use of the improper part of a medicinal plant species can lead to ineffective, or even harmful, outcomes. For these reasons, authentication is needed to be strict at all stages of harvesting and making formulations. Many methods are used for herbal drug authentication, including a wide-range of taxonomic, microscopic, genomic, proteomic, chemical and molecular techniques. Spectroscopy, including Diffuse Reflectance (DRIFT) and Photo-Acoustic Spectroscopy (PAS) are particularly advanced procedures that are recommended for characterization. The widespread issues of substitution and adulteration, especially in the case of wild-collected crude drugs, highlight the need for standardized procedures. Further, many medicinal plants are shared or sold under a common vernacular name which leads to misidentification since multiple species may be marketed under the same name.

On the other hand, multiple names can designate a singular species, which contributes to the process of botanical authentication becoming complex. If scientific verification is performed, the investigation should involve measuring the bioactive elements responsible for any claimed therapeutic effects. Factors like biotope, soil composition, and climate determine phytochemical content, as demonstrated by variable artemisinin production in *Artemisia annua*. Furthermore, medicinal plants obtained from contaminated sites have been shown to concentrate heavy metals, raising safety concerns. More seriously, environmental degeneration has the potential to not only affect the amounts but the combination of bioactive components which determines the therapeutic effect. Standardization of herbal drug characterization is achieved through the examination of morphology, anatomy, chemical profiling (ash, extractives, loss on drying), and various DNA fingerprinting techniques. The Unani Pharmacopoeia of India organizes a significant number of phyto-drugs based on plant part, and provides a brief account of botanical identification, chemical composition, therapeutic uses, and formulation to maintain scientific rigor [25].

Adulteration and misidentification in herbal medicines

Adulteration is a form of unethical practice characterized by the intentional addition of impure or inferior substances to herbal medicines, including synthetic pharmaceuticals, lower quality plant materials, or other materials such as sand or metals. Adulteration of herbal products has been documented in several studies, with some products openly containing drugs like sildenafil. Adulteration can happen during production of a product as a means to enhance profit margins. In many countries around the world, use of a combination of herbal and synthetic drugs is permitted by law. However, such products are not considered herbal medicines by the World Health Organization. Strict regulations and enforcement are critical to address the issue of adulteration and protect the safety of herbal medicines. Here the adulterant types with examples are mentioned in (table 1& 2).

Unintentional adulterant (Misidentification & accidental substitution)

Adulterant	Intended plant	Risk
Aristolochia species **(e.g., *Aristolochia fangchi*)**	*Stephania tetrandra* ("Fangji")	Contains aristolochic acid, which is nephrotoxic and carcinogenic.
Caulis Aristolochiae Manshuriensis	*Caulis Akebiae* ("Mutong")	Causes aristolochic acid nephropathy.
Digitalis lanata	*Plantago species* (Plantain herb)	Contains cardiac glycosides, which can be toxic to the heart.
Atropa belladonna	*Solanum nigrum*	Contains tropane alkaloids that are toxic even in small amounts.
Clerodendrum inerme	*Gymnema sylvestre*	Incorrect substitution can affect blood sugar regulation.

[TABLE NO. 1]

Intentional Adulterants (Fraudulent replacement for financial advantage)

Adulterant	Commonly Adulterated Product	Risk
Sildenafil (Viagra)	Herbal aphrodisiac formulations	Can cause severe cardiovascular effects, especially in people with heart conditions.
Dexamethasone or corticosteroids	Herbal anti-inflammatory medicines	Long-term use leads to adrenal suppression, osteoporosis, and immune suppression.
Cheap starches or foreign plant powders	Expensive herbal powders (e.g., turmeric)	Reduces efficacy and may introduce toxic compounds.
Lead and mercury salts	Ayurvedic and traditional medicines	Can cause heavy metal poisoning, leading to neurological and kidney damage.
Papaya seeds	Black pepper	Economic fraud; may not cause harm but lacks medicinal properties.
Strychnos nux-vomica	Herbal tonics	Contains strychnine, a potent neurotoxin that causes convulsions.

[TABLE NO. 2]

Misidentification

It takes place inadvertently when an herb is identified incorrectly for another herb due to a mislabeling, similarities in appearance, or confounding names. Many herbs have identical names or local names notwithstanding the fact that they are not part of the same botanical family, creating difficulties and health consequences, such as aristolochic acid nephropathy from misidentified herbs. The situation is further compounded by historical information, language differences and a lack of taxonomic uniformity. Reliable identification may require the use of modern analytical techniques, and organizations such a WHO are presently engaged in an effort to standardized botanical nomenclature to avert these problems [26, 27].

Standardization and evaluation of active ingredients

1. Organoleptic, macroscopical and microscopical test

The identification of a plant or the preparation can be performed by using sensory evaluation including visual inspection, smell, tasting, and touch. A macroscopic evaluation of herbal drugs involves assessing important physical characteristics of the drug, including shape, size, colour, surface characteristics, fracture characteristics, or characteristics of the internal cut surface. A microscopic evaluation examines histological characteristics observed under the microscope, either with or without the use of chemical reagents. Once again, this step is an important step to verify the identity and purity of herbal drugs, which is why comparing these characteristics with an authenticated reference sample is very important. Whenever possible, authenticated

specimens that are compliant with pharmacopoeias active ingredient specifications should be used for reference materials.

2. Foreign matter

Foreign matter encompasses any non-target material found in samples of medicinal plant materials, including non-target plant matter, biological contaminants, or mineral impurities, such as stones, sand, or dust. Their identification and quantification can be performed through macroscopic and microscopic examination of the plant material.

3. Determination of Water and Volatile Content

The quantification of moisture and volatile content in plant materials are determined through thermo gravimetric methods. For finely powdered samples, Karl Fischer titration is a reliable method of accurately measuring water content. This measurement is especially necessary for dried material as excessive moisture promotes microbial growth, which can degrade the sample material.

4. Analysis of Ash and Its Importance

The analysis of ash provides an estimation of the inorganic constituents of plant materials. Ash analysis can also facilitate the detection of contamination or adulteration of the original plant materials. There are four distinct types of ash that are measured:

•**Total ash** is performed on plant materials that contain little to no calcium oxalate as found in a sample of ginger.

•**Acid insoluble ash** is conducted to signify excessive soil contamination.

•**Water soluble ash** is performed specifically for standardizing samples of ginger.

•**Sulphated ash** can demonstrate the presence of non-volatile inorganic impurities, with examples including the detection of alkali metals.

5. Residue Evaluation of Pesticides and Herbicides

Agricultural activities (e.g., spraying, soil immersions, and/or fumigation) can leave residues of pesticide and/or herbicides in the plant material. Compounds of concern relate to organic chlorides, organophosphates, and carbonates, and pesticides obtained from other plants like pyrethrum. Residues must occur in acceptable ranges, and analysis is usually done using gas-liquid-chromatography.

6. Haemolytic Activity Test

It should be done for any plants containing saponins, particularly DioscoreaSceae, Araliaceae, Cryophyllaceae, Sapindaceae, or plants in the Primulaceae families. Haemolytic activity testing ensures that plant material will not cause lysis of erythrocytes when used in a medicinal form.

7. Foaming Index

In plants containing saponins, an aqueous extract or decoction should be analysed for foaming index. The presence of foaming can complicate preparation and dosing, making this testing for foaming index essential for standardization and formulations.

8. Loss on Ignition

Loss on Ignition tests plant material containing a significant portion of tightly held water. It assesses the total amount of volatile component(s) released upon combustion, which provides characterization information for the plant material.

9. Testing for Heavy Metal Contamination

Heavy metal contamination can occur in medicinal plants due to environmental pollution, with arsenic and lead being the most frequent. Lead is typically found to be elevated in the plants collected in areas near highways or industrialized areas that use fossil fuel. Testing for heavy metals is an important set of limit tests that are critical for safety and compliance.

10. Microbial Load and Pathogen Testing

To reduce microbial contamination during the harvest and processing of medicinal plants, it is essential to implement an appropriate degree of hygiene. Testing should occur to rule out the presence of pathogenic bacteria and fungi in herb preparations, using techniques similar to those applied to other pharmaceutical drug testing. Testing for the absence of harmful organisms will reduce spoilage and ensure consumer safety.

Quantifying active ingredients

Quality control of herbal medicines can be challenging, especially regarding the quantification of active ingredients. Each type of preparation will have a different approach, depending on the use of active ingredients, semi- purified extract, or crude plant material. Since plants produce medicinal and non-medicinal ingredients, the assessment of quality often involves measuring the level of herb active or marker compounds; using motion-ion chromatography techniques such as thin layer chromatography, liquid chromatography, and gas chromatography. Qualifying active ingredients is more complicated in a multi-herb formulation, but developments in standardization have made it possible to produce viable herbal medicine quality aspects [28, 29].

Quality control considerations for herbal medicinal product

The quality assurance of herbal medicines, which are products of plant origin, is of utmost importance to ensure consumer safety and therapeutic benefit. However, the regulatory burden and requirements for quality assurance with herbal medicine are somewhat limited compared to drug standards. This creates a significant risk for adulteration and substitution regulated herbal medicines and herbal dietary supplements can pose a potential risk to health and safety. Quality can be either assured by standardization, phytochemical development, and analytical techniques such as chromatography or spectroscopy [30].

Common methods of Quality Control are:

A. Standardization and Authentication

• This incorporates methods of ensuring that herbal medicines are within their predetermined qualitative and quantitative limits prior to being considered manufactured herbal products or herbal dietary supplements. Methods of standardization and authentication include organoleptic, microscopic and physicochemical measurements.

B. Chromatographic Methods

• HPTLC (High-Performance Thin-Layer Chromatography): Utilized to separate, identify, and quantify phytochemical constituents to verify authenticity and for quality assurance [31].

• HPLC (High-Performance Liquid Chromatography): Utilized to separate, identify, and quantify pharmaceutical or bioactive constituents in herbal drugs or herbal medicine with a great degree of accuracy.

• SFC (Supercritical Fluid Chromatography): Utilized as a form of green science to study lipids, flavonoids, and other herbal pharmaceutical constituents where less solvent is utilized, compared to traditional chromatographic methods [32, 33].

C. Spectroscopic Techniques:

- ICP-MS (Inductively Coupled Plasma-Mass Spectroscopy): This technique determines the presence of trace and heavy metals in herbal medicines in order to assess safety. - LC-MS (Liquid chromatography-Mass Spectroscopy): A detection/analysis fidelity, sensitivity and multi-component method of analysis.

- GC-MS (Gas chromatography-Mass Spectroscopy): Utilised to analyse the essentials oils and volatile compounds of herbal medicine formulations [34].

D. Thermal Analysis: - TGA (Thermo gravimetric Analysis) & DTA (Differential Thermal Analysis): Measures the thermal stability, mass changes and sensitivity of the product. As traditional medicine is increasingly accepted worldwide, it is important to use advanced analytical methodologies to ensure the quality and compliance [35, 36].

Processing and storage conditions

- Processing methods, such as drying, boiling, or extracting, can modify the chemical composition and pharmacological properties of these products.

- Herbal formulations have a shelf life, which is subsequently altered due to more than ambient temperatures, humidity and exposure to light to which bioactive compounds degrade.

- Establishing proper storage conditions and shelf-life determination still proves to be difficult for many herbal product.

Challenges and barriers in development and promotion of herbal drugs

Challenges in Herbal Drug Formulation and Stability

Herbal medicine is a relatively new aspect of evidence-based medicine. The challenges to the use of modern pharmaceutical methodologies in herbal formulations are numerous. Systematic research approaches in a manner that is compatible with modern scientific paradigms and traditional medical paradigms are vital. Stability is one of the major challenges in herbal drug development. Stability testing demonstrates that the quality, safety, and efficacy of a drug will remain effective through time

and under diverse storage conditions. It is more challenging to maintain stability of herbal products compared to synthetic pharmaceuticals, due to the chemical diversity of raw materials, variability in biochemical properties, selection of appropriate stability markers, and naturally-occurring enzymes found in herbal formulations.

Limited Pharmacokinetic Data on Herbal Drugs

The pharmacokinetics of any drug—how it is absorbed, distributed, metabolized, and excreted—play an important role in determining its dosage, route of administration, and therapeutic effect. Data from preclinical studies and clinicians and trials provide the information necessary to judge a drug's safety and efficacy to support a reasonable benefit: risk assessment. Unfortunately, for herbal drugs, there is usually little to no data on pharmacokinetics, which allows for their use without persuasive dosing regimens. Also, the interaction of herbal drug with conventional pharmaceutical products may result in an unexpected lack of efficacy or an adverse event; both of which can be a barrier to the clinical use of herbal products.

Regulatory challenges in herbal medicines development

Regulatory approaches to herbal medicines vary, which may be defined differently in different countries. Where herbal drugs are regulated as such, they are defined either as prescription or non-prescription medications. Furthermore, some herbal products may be considered (or classified) as dietary supplements. The lack of regulatory consistency does not allow for uniform regulations regarding access to herbal medicines and practice. Typically, the national regulatory framework outlines who can manufacture herbal medicines and determine what herbal medicines are accessible; this approach is not consistent worldwide. The difference in regulations presents another challenge for researching and developing herbal drugs.

Quality Assurance and Clear Expectations

Quality reassurance and expectancy of herbal products play an important role in the health benefits of an herb. National and regional pharmacopeia define the quality standards for many herbal products, including powdered extracts and essential oils in commerce. Because there are many variables that influence the quality of herbal raw materials, such as geographic source, harvest, agricultural methods, and processing conditions, it is very complicate to define, categorize, or simply compare the quality of herbal products. Countries that formally regulate herbal medicines should create and uphold strict practices for quality assurance and practice, including Good Manufacturing Practices (GMP), product labelling, licensing, and importing requirements that ensure consumer safety and transparency.

Ethics and Methodology Issues in Clinical Trials

One of the most challenging aspects of clinical trials for herbal drugs is dealing with financial constraints, ethical issues, inherent challenges, preparing a rigorous study design, and regulatory demands. Many herbal medicines have, by use, been accepted for centuries, leading to presumptions of safety and efficacy. However, the absence of formal quality assurance practices along with existing pharmacological, pharmacokinetic, or clinical data are all contributors to successfully using these medicines into modern practice. One of the greatest barriers to overcoming conducting a clinical trial for herbal drugs is the need for consistency across batches of herbal products. In many cases, herbal formulations contain numerous active compounds that vary in concentration, and researchers must monitor this situation in preparation for their studies. Creating placebo-controlled investigations of herbal medicines presents unique challenges, for all herbal products possess unique sensory characteristics (e.g., colour, taste, and odour). Remodelling a placebo for an herbal drug such as ginger, and its uniquely distinctive smell, is difficult. Selecting the control groups in clinical trials is also difficult. Control groups must match treatment groups closely hence meaningful comparisons can be made. Treatment appearance, administered frequency, and patient belief in the treatment must be taken into account for trial validity. In many cases, although these caveats remain possible, the modern arena of clinical investigation, with external regulatory influence on quality control standards and rigorous trial design, has addressed these issues better.

The Role of Patient Compliance and Psychological Factors

Patient compliance and psychological factors often mediate the therapeutic efficacy of traditional herbal treatments. Many herbal therapies prescribe complicated treatment regimens with multiple active ingredients and specific treatment instructions. Placebo effects, and the credibility the therapist provides, can factor into perceived therapeutic efficacy for herbal therapies. Therefore, adherence and patient motivation is imperative for achieving therapeutic efficacy. The rigorous designs of modern clinical trials, such as blinding and randomization, can mitigate bias and improve study reliability [37, 38].

Findings and discussion

A. Difficulty with Herbal Medicine Standardization and Quality Assurance

Quality assurance and standardization poses a major challenge for the acceptance of herbals. Herbal medicines do not have a standardized framework for formulation or quality assurance, unlike synthetic pharmaceuticals that go through an extensive external review process. An issue with herbal medicines is the variability of starting plant material (e.g. roots, leaves, etc.). The raw plant material can differ in its herbal compounds as a result of a number of environmental conditions (e.g. climate, soil quality, altitude, etc.), as well as seasonal variability. Analytical methods such as **HPTLC, HPLC, SFC and ICP-MS** are helpful for batch-to-batch consistency of active compounds in herbal formulations.

B. Adulteration and Mislabelling of Herbal Medicine

Adulteration of herbal drugs is a significant problem for the manufacture of herbal drugs. Adulteration could be due to an intentional substitution of substandard ingredients or an unintentional labelling issue with a misidentified plant species. A number of research studies indicate that herbal products are adulterated and/or contain adulterated products at significant rates. For example, some herbal products have been found to contain pharmaceuticals **(e.g. corticosteroids; sildenafil, etc.)** which provide potential health risks. The issue of mislabelling of herbal products may lead to a similar herb being in the product, but it may not confer the same therapeutic effects. Techniques such as **DNA fingerprinting, DRIFT methods, and PAS** are identified as advanced spectroscopic and genomic methods that are considered applicable to authentication of plant species in herbal medicine, and drug manufacturing.

C. Challenges in Pharmacokinetics and Bioavailability

The pharmacokinetics of herbal medicines remains poorly understood, and therefore remains a complication in the standardization of doses and assessment of therapeutic efficacy. This is complicated by the presence of multiple active drug constituents in natural herbal medicines, leading to uncertainty in pharmacodynamics interactions. Additionally, the minimal number of studies **on absorption, distribution, metabolism, and excretion (ADME)** for herbal compounds has limited their use in clinical practice. Future research combining **genomics, proteomics, and metabolomics studies** may be useful to elucidate possible active metabolites and identify formulations of herbal drugs with improved pharmacokinetic profiles and bioavailability.

D. Regulation of Herbal Medicines

There are significant differences in the regulatory environment for herbal medicines around the world, with some countries considering herbal medicines, dietary supplements rather than pharmaceutical drugs. Herbal drugs are governed **in India under the Drugs and Cosmetics Act (1940).** These discrepancies in the recognized scientific basis of herbal medicines complicate trade and acceptance. The development of globally harmonized regulations is paramount to trading safe and effective herbal medicines. For example, building regulations around standardizing the **pharmacopeia's, good manufacturing practices (GMP), and heavy metal limits** will support acceptance and access, which is needed.

E. Ethical Issues and Difficulties in Clinical Trials

The ethical and methodological challenges of conducting **RCTs (randomized controlled trials)** using herbal medicine can be complex. Herbal medicine is difficult to evaluate in RCTs with appropriate placebo controls because herbal medicine products employ multiples active constituents and this complexity complicates the creation of a placebo that looks, smells and tastes

the same as the active product. Techniques for randomization and blinding or concealment need to be carefully aimed at reducing bias. Compliance is another issue affecting the effectiveness of herbal medicine, and psychological issues surrounding hubs, fads and patient beliefs all contribute to the success of the herbal intervention.

F. Environmental and Storage-Related Variability in Herbal Medicine

The processing and storage of herbal drugs have substantial impact to their stability, efficacy and life of herbal medicines. Processing and storage conditions matter; the temperature, humidity and exposure to light can degrade bioactive compounds, herbs can be prepared by different extraction methods (hot or cold extraction using water, alcohol or ether), even the extraction method changes the chemical profile. Sound, standardized storage conditions and more advanced analysis, such as TGA and DTA, are essential for determining shelf life and stability.

G. The Future of Herbal Medicine and Integration with Modern Medicine

These research advancements present different opportunities for discovering new drugs using herbal materials despite the difficulties faced. Adverse effects of herbs are often underestimated, but promoting tradition to join forces with biotechnology, nanotechnology, and model-based drug discovery will produce benefits for drug discovery by improving ways to identify active fractions and products and better methods for formulation. Increased funding for computer modelling, harmonization of regulation of agents, and improving the integrity of clinical trials will help to place herbal compounds in an effective position for global acceptance as drugs against major and chronic health conditions.

CONCLUSION

This study clearly illustrates the immediate need for proper standardized quality testing and control procedures, further and better clinical studies, and uniformity of research across regulations for an overall safe and effective use of herbal medicine. The use of analytically advanced instrumentation, genomics, and metabolomics techniques can address variability associated with herbal medicine studies. Addressing the limitations of using pharmacokinetics, facing the ethical challenges of performing clinical studies, and considering each country or location's environment will improve the trust in herbal drugs, as credible medicine. All future opportunities will require collaboration and cooperation among researchers, regulatory agencies, and pharmaceutical industries, in order to realize the total medicinal potential of plant-derived drugs, globally.

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