

Transforming herbal medicines: Integrating traditional knowledge with modern pharmaceutical advancements

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ABSTRACT

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Herbal medicines have been known for centuries for healing and maintaining human health; according to the WHO, over 80% of the world's population relies on them for primary healthcare. Different countries and cultures have their own traditional medicine systems that utilize natural products, and humans have utilized that vast reservoir of knowledge for the benefit of society. Over time, the availability of standardized conventional medicines has decreased interest in herbal medicines. However, following the emergence of life-threatening viral diseases, interest in herbal medicines has resurged, leading to their increased use as remedies or for preventive purposes. However, the inconsistent quality, arising from issues such as authenticity, geographical origin, species variation, and a lack of quality control, has cast doubt on the efficacy of these natural treatments. Currently, advancements in sophisticated techniques for establishing herbal standards, including modern extraction technologies such as supercritical fluid, ultrasound-assisted and microwave-assisted extraction; analytical tools like HPLC-MS, spectroscopy, and DNA barcoding; and *in silico* approaches such as computational drug screening and network pharmacology, have renewed interest in herbal medicines. Historically, herbal medicines were prepared in traditional dosage forms, which have evolved into standardized preparations through scientific advancement. Modernizing the field through the development of nano-formulation, the enhancement of extraction and analytical techniques, and the application of DNA fingerprinting, biotechnological screening, and computational methods is establishing pharmacological efficacy and standardization. These innovations provide the proof of concept needed to convert ancient knowledge into modern remedies. Various formulation approaches, representing pharmaceutical innovations in herbal medicines, have been found to increase bioavailability by up to 5-50 times and improve the stability of dosage forms, resulting in enhanced efficacy. Recognizing these advancements, many countries have begun to regulate herbal products similarly to conventional medicines, implementing standards such as good manufacturing practices. The herbal market is expected to reach \$437 billion by 2032, and these developments, combined with regulatory improvements, are assisting herbal treatments in gaining international recognition. Although herbal products are generally regarded as safe, multidisciplinary studies are needed to validate their safety and efficacy. Establishing clinical efficacy through clinical trials should be a primary focus of future research. With these innovations, herbal medicine holds the potential to address many challenges associated with chronic and communicable diseases.

Keywords: herbal medicines; nano-formulation; quality control; chromatography; spectroscopy

1. INTRODUCTION

Traditional herbal medicine, an ancient science, is a gift from nature that utilizes natural products as therapeutic and healing agents. This practice is foundational to many established systems, including Ayurveda, Siddha, traditional Chinese system, traditional Korean medicine (TKM) and Unani (Kim et al., 2020; Matos et al., 2021; Zhang et al., 2021a). For centuries, people across the globe have utilized natural products, incorporating them into their traditional practices. Over time, these practices have evolved into well-structured and regulated systems of medicine. While these systems may have certain shortcomings they hold immense value as a reservoir of human knowledge (Fabricant & Farnsworth, 2001; Alves & Rosa, 2007). Indian, Chinese, South American, and Egyptian cultures continue to rely on plant-based therapies for treating various diseases. According to the World Health Organization (WHO), around 60% of the global population uses herbal medicine, with nearly 80% of people in developing countries depending on it almost exclusively for primary healthcare (Ahmed Khan & Ahmed, 2019). Reflecting this sustained demand, the global herbal medicine market was valued at USD 233.08 billion in 2024 and is projected to grow at a rate of 8.23% from 2025 to 2032, reaching approximately USD 437 billion. In 2024, Europe accounted for the largest market share, at 44.55%. Meanwhile, the U.S. market is expected to reach USD 37.90 billion by 2032. This growth is driven by increasing health awareness, a preference for natural products and ongoing scientific advancements in herbal extraction and formulation. Consequently, approximately one-third of the most widely used pharmaceuticals are derived from natural sources (Ahmed Khan & Ahmed, 2019; Bhoi et al., 2023; Chaachouay & Zidane, 2024). However, pharmaceutical companies face challenges in developing herbal formulations due to limitations associated with herbal drugs and a lack of comprehensive knowledge regarding their applications to modern ailments such as cancer, antimicrobial resistance, viral infections, cardiovascular, obesity, and diabetic disorders (Atanasov et al., 2015; Mundy et al., 2016; Caesar & Cech, 2019). Additionally, challenges include inconsistent formulations resulting from factors such as geographic diversity, biodiversity, and seasonal variations in the active components of herbal medications (Baker et al., 2007; Sen et al., 2011). Furthermore, the isolation of phytoconstituents and the discovery of drugs from natural sources are associated with relatively high expenses (Yuan et al., 2016). The limited solubility of vital bioactive components in water or lipids, poor permeability through biological membranes, and restricted bioavailability present significant hurdles (Lao et al., 2006). These issues affect many potent active phytoconstituents, including curcumin, eugenol, embelin, betulinic acid, berberine, boswellic acids, silymarin, piperine, flavonoid derivatives, resveratrol, andrographolide, and plant extracts from plants such as *Moringa oleifera*, *Ginkgo biloba*, *Curcuma longa*, *Bacopa moniera*, and *Allium cepa*.

To address the limitations of the traditional herbal preparations, conventional dosage forms such as capsules, tablets, syrups, and suspensions were developed to improve the effectiveness of herbal and Ayurvedic medicines (Elkordy et al., 2021). Yet, current innovation in the study of traditional medicine has led to significant

modernization through the emergence of new technologies, such as nanotechnology (Ansari & Husain, 2012; Patra et al., 2018). The benefits of advanced technologies in medical science have been demonstrated in a range of areas, such as artificial implants, biosensors, tissue imaging, nanorobotics, and advanced drug delivery systems, including targeted and sustained-release formulations (Farooq et al., 2019a). The prefix 'nano' in pharmaceuticals or formulations signifies drug particles in the 10–1000 nm size range. However, particles larger than 200 nm are typically eliminated from the circulation, by the lymphatic system (Jeevanandam et al., 2016). Hence, nanoparticles (NPs), with diameters from 10 nm to under 200 nm, are considered optimal for effective drug administration (Hoshyar et al., 2016; Rizvi & Saleh, 2018). NPs possess distinct magnetic, chemical, structural, mechanical, and biological characteristics, that enhance their mobility in the body compared to larger particles (De Jong & Borm, 2008). NPs have extensive applications in various biomedical domains, including diagnosis, imaging, and drug delivery. The concept of nanomedicine has historical roots in Ayurveda, the traditional Indian system of medicine that utilizes metal-based NPs, such as Bhasma, for therapeutic applications (Arvizo et al., 2012; Sharma & Prajapati, 2016; Zhang et al., 2021a). The process of creating Bhasma (ash) is referred to as 'Bhasmikarana'. During this process, metals and herbal extracts undergo calcination, transforming them into therapeutic NPs, often through changes in their oxidative state. These metallic NPs exhibit improved absorption, stability, and biocompatibility. Various metals such as Hg (mercury, Parada), Fe (iron, Loha/Aayasa), Sn (tin, Vanga), Zn (zinc, Yasada), Pb (lead, Naga/Sisaka), Cu (copper, Tamra), Au (gold, Swarna) and Ag (silver, Rajata) are frequently employed in the preparation of Dhatu Bhasma (Farooq et al., 2019b). These metal-based NPs, often containing various phytoconstituents, can enhance therapeutic efficacy through improved absorption and tissue targeting, with their nanoscale size being a key contributor to this increased effectiveness (Sarkar & Chaudhary, 2010; Pandey et al., 2015; Ambwani et al., 2018). Overall, Bhasma is highly relevance to contemporary nanomedicine and serves as a historical paradigm for the advancement of modern nanoformulations (Pal et al., 2014).

The convergence of traditional medicine and nanomedicine represents an interdisciplinary approach to enhancing therapeutic efficacy and promoting human health. Various herbal medications and/or their active ingredients have been utilized to develop and optimize diverse nanodrugs. Various nanoformulations, including polymeric and metallic NPs, nanoemulsions, phytosomes, ethosomes, liposomes, dendrimers, and micelles, have been developed to deliver herbal remedies (Teja et al., 2022). Among these, polymeric NPs, nanoemulsions, and phytosomes have emerged as the most common nanoformulation approaches for herbal medicines (Moradi et al., 2020). Despite the development of numerous herbal nanoformulations, there remains a lack of clear guidance on selecting the appropriate nanocarrier for specific classes of active ingredients or extracts. Additionally, standardized methods for the development, characterization, and quality control of herbal nanomedicines are still lacking. Therefore, this review comprehensively examines the aforementioned knowledge gaps, provides an overview of the evolution of herbal medicine, and discusses the

challenges in developing novel herbal formulations. Furthermore, it underscores the significance of herbal nanomedicines as a modern solution for optimizing therapeutic outcomes while minimizing potential adverse effects (Ansari et al., 2012). The information compiled in this review was obtained from scholarly articles, books, patents, and scientific databases (e.g., SciFinder, Science Direct, PubMed, ACS, and MedlinePlus) (Teja et al., 2022). The data underwent a thorough critical analysis to evaluate how different nanoformulation strategies alter key pharmacokinetic and physicochemical parameters, such as bioavailability, solubility, stability, and bioactivities, of the herbal compounds.

2. HISTORICAL PERSPECTIVES OF HERBAL MEDICINE

The history of herbalism is tightly connected with the evolution of medicine, bridging the period from ancient times to the 19th-century emergence of the germ theory of disease. Modern medicine, which began in the 19th century, relies on evidence collected through the scientific method for treating various chronic diseases (Sakai & Morimoto, 2022). The utilization of evidence-based pharmaceutical drugs and phytoconstituents, often derived from medicinal plants, has largely supplanted traditional herbal remedies in contemporary healthcare (Tanaka & Kashiwada, 2021). During earlier periods, sources of medication primarily included drugs or phytoconstituents obtained from mineral, plant, marine, and animal sources. Interestingly, certain plants possess the capability to treat diseases and rejuvenate bodily systems (Dubey et al., 2004). While identifying the precise historical origin of specific medicines is difficult, many traditional remedies have been developed into novel formulations for treating life-threatening diseases (Min et al., 2008). Historical records indicate the use of medicinal plants in civilizations

such as India, China, Egypt, Greece, and Babylon as early as 5,000 years ago (Yen et al., 2009). A timeline of the historical perspectives of herbal medicine is shown in Figure 1. The Greeks pioneered important medical concepts such as prognosis, diagnosis, and advanced ethical principles within the field of medicine. The Hippocratic Oath, authored in Greece during the 5th century BCE, had a direct influence on the oaths taken by modern physicians upon entering the medical field. In earlier times, surgical techniques passed down from ancient experts were refined and systematically structured, a process demonstrated in Rogerius's treatise 'The Practice of Surgery' (Pellegrini & de Santibañes, 2019). The training of physicians commenced in Italian universities around 1220. The Renaissance saw enhanced anatomical understanding and the invention of the microscope.

The 19th century germ theory of disease facilitated breakthroughs in treating infectious ailments. Military doctors advanced trauma treatment and surgical techniques. Rapid urban growth necessitated structured sanitary measures, leading to the development of public health strategies. The early 20th century saw the establishment of advanced research centers, often linked to major hospitals. The mid-20th century marked the introduction of new treatments in biological disciplines, such as antibiotics. These advances, along with developments in genetics, radiography, and chemistry, laid the foundation for contemporary medical practices. The 20th century saw the professionalization of medicine, with new opportunities for women in nursing (starting in the 1870s) and physician roles (particularly post-1970). Despite these developments in modern medicine, the use of herbs for pharmacological treatment has ancient roots (Schulz et al., 2001). Folk healing practices across many cultures incorporate herbs. In recent times, there has been a renewed scientific and public interest in the importance and potential benefits of herbs, which are now gaining prominence on a global scale.

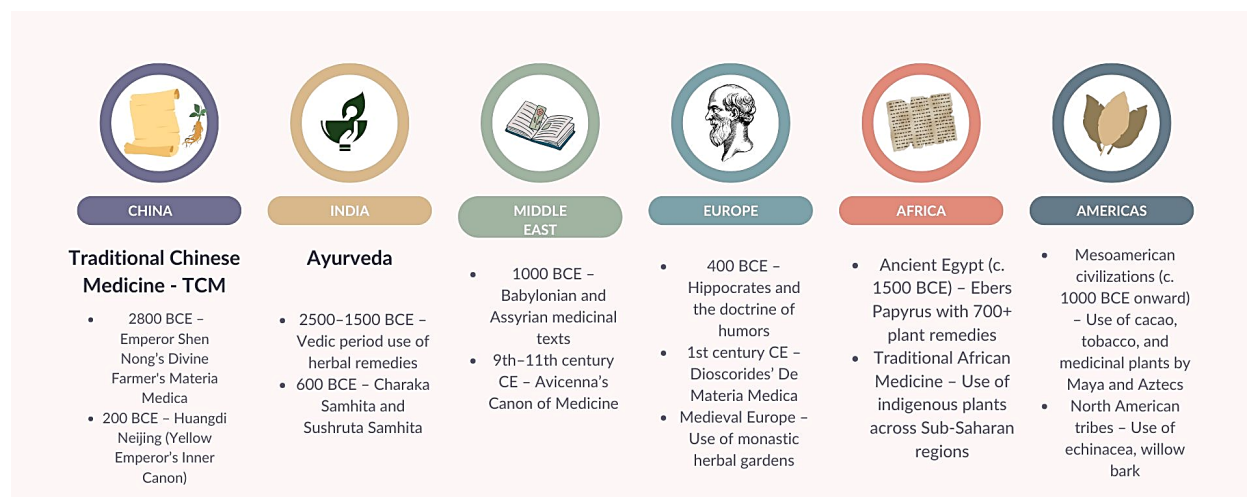


Figure 1. Herbal medicine through the ages: A global timeline

2.1 Traditional uses of medicinal plants

The application of plants as fundamental sources of remedies and treatments is deeply embedded in diverse traditional medicinal systems. In recent times, an increasing number of individuals are turning towards plant-based medicines and products to enhance their well-being, either as standalone treatments or in conjunction with other therapies. The WHO highlights the broad reliance on herbs and plant-based solutions for addressing fundamental healthcare needs (World Health Organization, 2004). Herbal medicine encompasses not only whole herbs or plant parts but also processed and refined herbal products, along with their active constituents. In recent times, there has been a significant resurgence in the popularity of herbal products (Pan et al., 2014). This resurgence can be attributed to concerns over the adverse effects of conventional pharmaceuticals, the failure of modern treatments for chronic conditions, and growing antibiotic resistance. Notably, almost three-quarters of plant-based therapeutic entities used worldwide originated from traditional medicine practices. In India, approximately 70% of traditional and modern drugs are either synthesized from or directly obtained from natural sources (Pandey et al., 2013). The traditional healing practices of India utilize a wealth of botanical diversity, with a vast array of plants being employed. For instance, it is estimated that Ayurveda uses approximately 1,200–1,800 plant species, Siddha medicine draws upon 500–900 plants, and Unani medicine incorporates around 400–700 medicinal plants. Folk healers across India utilize over 7,500 medicinal plants across various systems (Ved & Goraya, 2011; Debnath et al., 2015). Herbal medicines have demonstrated various therapeutic benefits within the healthcare system. For respiratory diseases, active compounds like berberine, curcumin, tulsi, and essential oils can help ease inflammation and improve breathing. Cardiovascular health is supported by agents such as curcumin, alliin, allicin, cinnamaldehyde, and resveratrol, which improve lipid profiles by reducing LDL, TG, and VLDL levels. Anti-inflammatory effects are attributed to the consumption of antioxidant-rich compounds like gallic acid, flavonoids, and vitamin C. Anticancer properties are seen in natural compounds like paclitaxel, crocin, vincristine, and curcumin, which can inhibit tumor growth. Neuroprotective effects are provided by compounds such as ginkgolides, bacoside A, withaferin A, and curcumin, which aid in cognitive support and neural protection. Many other active herbal compounds can also play a role in maintaining the balance of various body systems, contributing to overall health and wellness (Wink, 2015; Gonfa et al., 2023).

2.2 Evolution of herbal medicine in different cultures

The origins of modern herbal medicine can be traced to traditional medicine (TM), the most ancient form of healthcare worldwide. Historically, TM served as a means of preventing, managing, and treating both physical and mental ailments. Throughout history, diverse societies created unique healing approaches to combat a wide array of life-threatening conditions (Abdullahi, 2011). As a result, herbal drugs remain widely used in many healthcare systems, valued for their potential efficacy against various diseases. The various forms of herbal prodrugs, including health supplements, cosmetics,

nutraceuticals, and phytopharmaceuticals, are in high demand globally, often due to a public perception of greater safety, affordability, and availability compared to synthetic drugs (Dubey et al., 2004; Sharma & Chow, 2008). These approaches, commonly known as traditional and complementary/alternative medicine, retain their importance in numerous countries, as demonstrated by their ongoing use (World Health Organization, 2000; Abdullahi, 2011). The basis of TM relies heavily on herbal medicine, in which natural substances play a central role in healing. These botanical compounds, acting either individually or synergistically, yield the intended pharmacological effects (Li-Weber, 2009). Within TM, a single herb or a formulated mixture can contain a myriad of phytochemical components, including alkaloids, glycosides, phenolic compounds, flavonoids, terpenoids, and others (Li-Weber, 2009). Notably, a comprehensive inquiry was conducted under the WHO's Traditional Medicine Program. This investigation examined national pharmacopoeias alongside global scientific literature (Abdullahi, 2011; Parasuraman et al., 2014).

Medicinal plants play an important role in traditional systems worldwide, from the Americas to the Arabian countries. Throughout history, herbal drugs have been documented in various medicinal systems, including Chinese, Indian, Greek, Egyptian, Thai, and Roman traditions, spanning approximately 5,000 years (Table 1).

Ayurveda, Thai, and Chinese systems of medicine share common traits, primarily aiming to improve the quality of life for patients through disease prevention and rehabilitation by balancing the body's systems. However, these systems are not limited to patient care alone. For example, TCM operates on the principle of 'Yin and Yang', opposing forces in nature that must be balanced to preserve a patient's health and well-being. This balance is achieved through the regulation of bodily fluids and internal organ systems. When there is a lack of balance between the two energies, sickness arises. The physician considers this principle when providing medical care. Botanical remedies and other therapeutic interventions are employed to rectify this yin-yang disharmony (Gibert-Tisseuil, 1998; Cheng, 2000).

In Ayurveda, the universe is traditionally believed to be composed of the five elements: ether, air, fire, water, and earth. These elements are interconnected and originate from ether, with each subsequent element evolving from the previous one. Consciousness is associated with ether due to shared qualities like clarity and expansiveness. Ayurveda utilizes these elements for healing by recommending specific approaches based on individual imbalances. The theory of Tridoshas in Ayurveda involves three energies known as vata (air + ether), pitta (fire + water), and kapha (earth + water). The balance of these energies is crucial for maintaining health, with their imbalance leading to diseases. Ayurvedic principles focus on restoring this balance through various means like diet, exercise, behavior, and medicine. Traditional Thai medicine (TTM) follows a holistic approach to healthcare, incorporating methods such as diagnosis, treatment, and Thai massage. This system is described as operating through a process of selection, adoption, adaptation, and utilization (SAAU). TTM practitioners aim to achieve equilibrium between different bodily systems by administering traditional remedies to restore health.

Table 1. Evolution of herbal medicine in different cultures

Name of traditional medicine	Origin	Concept or application	Current status	Advanced research
Traditional Chinese medicine (TCM) (Yuan et al., 2016; Lehmann, 2012; World Health Organization, 2000; Xue et al., 2013)	China	From a holistic view, it emphasizes mind-body interaction and the application of herbal drugs in acupuncture.	Out of 397 diseases, 11 major ones, such as cardiovascular disease, gynecology, pediatrics, ophthalmology, ENT, skin disease, SARS, and cerebral ischemia, were covered (Wang et al., 2016).	Methods include serum pharmacology and serum phytochemistry, biochromatography, network pharmacology, and proteomics, so as to provide references and information (Tang et al., 2022).
Ayurveda (Parasuraman et al., 2014; Patwardhan, 2014)	India	Works on the promotion and maintenance of health and the prevention of disease, and treatment.	It is conceptualized for preventive, therapeutic, meditative, recuperative, and rehabilitative features.	• Promoting interdisciplinary research • Establishment of standard operating procedures in the development of Ayurvedic dosage forms
Unani and Siddha medicines	India	Siddha is composed of metals and minerals from its sources. It identifies spiritual, mental, emotional, and physical reasons for illness and believes that each person should take responsibility for their own health.	There are 45011 registered Unani practitioners in the country. Currently, Unnani hospitals and dispensaries are available in 21 states in the country.	Numerous phytochemicals separated from mangrove plants are used in form of formulations for the treatment of diseases and surgery.

2.3 Challenges in herbal medicine

The advancement of herbal medicine faces diverse challenges worldwide, particularly in affluent nations, despite a shared global understanding and a robust history of traditional applications (Sahoo & Manchikanti, 2013). As the demand for herbal products increases, safety concerns become increasingly significant. To facilitate the global dissemination of traditional herbal knowledge, it is imperative to address the following obstacles (Bodeker et al., 2003; Thillaivanan & Samraj, 2014). Many adverse effects from herbal remedies may be attributed to poor-quality ingredients or manufacturing processes. Various forms of herbal treatments are associated with a range of issues such as, adulteration, contamination by heavy metals, and inconsistencies in phytoconstituent levels (Booker et al., 2012). The categorization of herbal medicines as food or dietary supplements by some governments is recognized as a primary contributor to the regulatory obstacles they face (Bandaranayake, 2006; Sen & Chakraborty, 2014). In many regions, traditional medicine practitioners lack proper registration or licensing. Furthermore, the effectiveness and safety of herbal remedies are often not substantiated through rigorous regulatory processes (De Silva, 1997; Ekor, 2014). Consequently, ensuring the safety of both traditional herbal remedies has become a primary public concern. Integrating traditional herbal knowledge into contemporary healthcare systems in a safe and effective manner requires careful attention to several key obstacles (Figure 2) (Booker et al., 2012).

2.3.1 Quality control

Herbal remedies are often not well-regulated, leading to issues such as a lack of standardization, poor-quality ingredients, manufacturing inconsistencies related to good manufacturing practices (GMP), and contamination with heavy metals or other harmful substances. This poses a significant challenge to ensuring the safety and efficacy of herbal products (World Health Organization, 2004). A lack of knowledge of quality control guidelines among cultivators and producers, as well as failures in implementation and enforcement, are common problems in the industry (Kunle et al., 2012; Shriwastav & Gupta, 2017).

Issues such as adulteration of powders, improper collection, and preparation of plant materials, contamination with heavy metals (Singh et al., 2011a), as well as the use of incorrect extraction and formulation processes, can compromise the effectiveness and safety of herbal remedies (Mukherjee et al., 2007).

2.3.2 Regulatory policies

The classification of herbal medicines as nutraceuticals or dietary supplements in some countries can lead to regulatory gaps, inadequate oversight, and difficulties in bringing these products to market (Abdel-Rahman et al., 2011). A lack of clear legal guidelines can hinder their safe and proper use (World Health Organization, 2005).

In some regions, traditional medicine practitioners may not be registered or licensed, leading to a lack of standardized training and qualifications. This can impact the quality of herbal treatments and undermine public trust (Saggar et al., 2022).



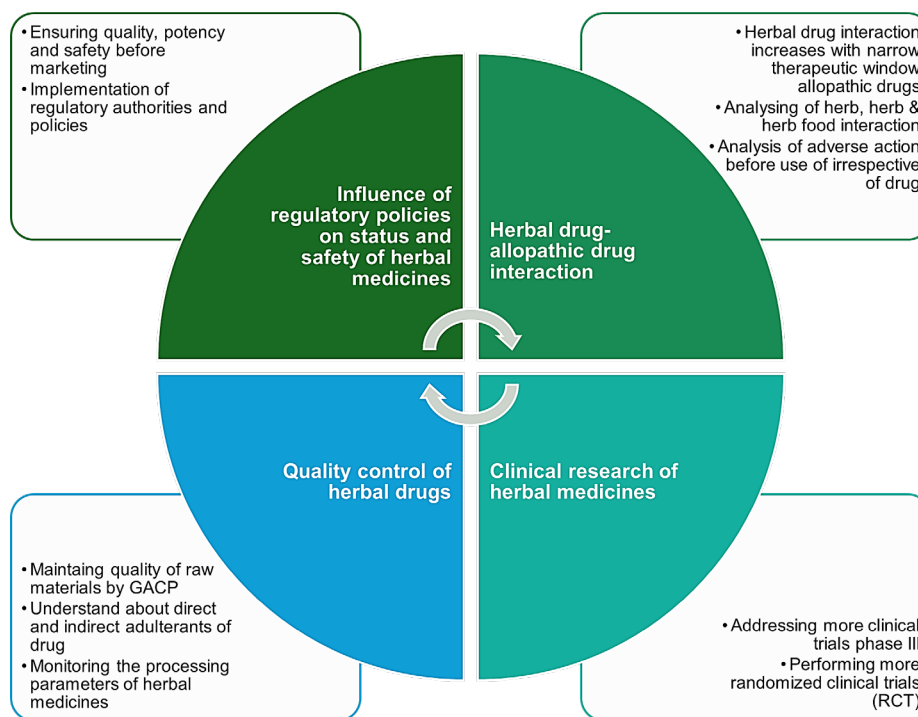


Figure 2. Challenges and suggestions related to the advancement of herbal medicines

2.3.3 Herb drug interaction

Herbs contain a wide range of active phytoconstituents, each with its own pharmacology, metabolism, and binding behavior (Zhou et al., 2013). There is a possibility of pharmacokinetic or pharmacodynamic interactions between these compounds and allopathic medications (Rombolà et al., 2020). The risk of drug interactions is particularly high for allopathic medications with a narrow therapeutic window, such as those used in chemotherapy, when co-administered with herbal remedies. Garlic and ginger, which can inhibit platelets and increase bleeding risk, should be avoided by people on warfarin (Leite et al., 2019). Adverse effects of herbal therapies may be caused by the use of incorrect plant species, adulteration, contamination with toxins or pharmaceuticals, overdose, and improper use by practitioners or consumers (Zhou et al., 2013). The safety of medicinal herbs is a concern for consumers, regulators, and medical practitioners, as analyzing adverse reactions is often more complex than for conventional drugs (Rodrigues & Barnes, 2013). The geographical origin of raw material, processing techniques, administration route, and potential interactions with other prescription pharmaceuticals complicate safety evaluations (Zhang et al., 2012). The authentication and collection of herbal materials for medicinal use are often challenging due to producers' lack of expertise in taxonomy and proper documentation (Farah et al., 2000). Standardized scientific nomenclature (including scientific synonyms) for herbal plants must be adopted to avoid confusion caused by regional or common names. For instance, *Artemisia absinthium* L. has at least 11 common names, many of which are not biologically descriptive (World Health Organization, 2004; Mordeniz, 2019).

2.3.4 Clinical research

Researching herbal medicines for large-scale, phase III clinical trials faces several obstacles, including economic

and ethical considerations, quality control, study design, and regulatory requirements for registering a new drug (Bansal et al., 2010). Blinding is the best approach for minimizing bias and mitigating placebo effects in randomized controlled trials (RCTs) (Misra, 2012). The selection of controls, calculation of sample size, and analysis of herbal formulations are the main factors affecting the outcome of clinical research.

2.4 Advantages of herbal medicine

One of the primary perceived benefits is that herbal medicines may cause fewer side effects, potentially making them suitable for long-term use compared to many conventional pharmaceutical treatments (Sahoo et al., 2009). Moreover, herbal medicines have demonstrated high effectiveness in treating both acute and chronic conditions. They are often recommended for extended use in managing chronic diseases, sometimes proving more beneficial than a single conventional medicine. For instance, Liv. 52 is a well-known polyherbal phytopharmaceutical formulation used in the treatment of liver disorders (Sam, 2019). Another notable advantage is their affordability; herbal medicines typically cost significantly less than allopathic drugs, especially those used for long-term treatment of chronic illnesses. This is partly because the processes involved in the development of synthetic drugs—such as invention, analytical testing, and advertising—greatly increase their overall cost. Lastly, herbal remedies are often more accessible, as many medicinal plants can be cultivated at home or found in local environments. Common examples include *Trigonella foenum-graecum* (fenugreek), *Mentha piperita* (peppermint), and chamomile, which are widely known for their therapeutic properties and ease of growth (Bhokare et al., 2016).

3. ADVANCEMENTS IN PHARMACEUTICAL TECHNOLOGY FOR HERBAL MEDICINE

Historically, the development of herbal formulations began with the identification of medicinal plants and the subsequent preparation of extracts. This process has evolved significantly; modern approaches now utilize *in silico* investigations and network pharmacology to identify active components or extracts for integration into innovative formulations. Furthermore, many herbal compounds undergo degradation in the stomach's acidic environment or extensive first-pass metabolism in the liver, which can prevent them from reaching their target site (Wei et al., 2020). If a drug fails to attain a minimum effective concentration at the target site, it cannot exert a therapeutic effect. Nanocarriers can transport an optimal dosage to the intended site of action, effectively circumventing obstacles such as degradation by stomach acid and first-pass liver metabolism. Their small size also facilitates extended circulation time in the bloodstream (Bairwa et al., 2010; Yadav et al., 2011).

3.1 Modern drug development techniques

The utilization of herbal medicines for addressing illnesses dates back thousands of years. In contrast to the conventional allopathic approach, herbal treatments encompass a multitude of active ingredients that collectively fight against diseases (Yadav et al., 2011). However, ensuring patient adherence requires delivery systems that can administer these components effectively over time, which is a primary goal of advanced drug development. Novel drug delivery systems (NDDSs) can enhance the therapeutic value by decreasing toxicity, and improving bioavailability (Dent & Matoba, 2020), while also reducing the administration frequency to improve patient compliance. The role of herbal medicines in drug development is substantial, as they serve as a reservoir of promising lead molecules (Singh et al., 2011b; Sungthongjeen et al., 1999). Many existing medicinal compounds originated from natural sources, with a notable emphasis on those derived from plants.

Over the past few decades, the pharmaceutical industry has paid limited attention to natural product drug discovery due to its inherent complexity (Tegtmeier et al., 2023). However, drug development from natural sources has recently experienced a resurgence of scientific interest driven by significant breakthroughs in technology. These advancements have played a crucial role in addressing the challenges associated with this area of research (Teja et al., 2022). This review provides an in-depth exploration of various steps from the selection, authentication, extraction /isolation, biological screening, and analogue development of plant-based natural compounds to the development of herbal formulations. A significant focus is placed on the bioactivity-guided fractionation technique, highlighting both its obstacles and the significant progress achieved (Carmona & Pereira, 2013). Furthermore, research suggests that the effective development of natural products requires an integrated interdisciplinary approach that incorporates technological advancements. These processes include effective selection methodologies, refined extraction and isolation procedures, sophisticated tools for structure elucidation, and high-throughput bioassays (Sardana, 2012). Contemporary

methodologies like molecular modeling, virtual screening, and database mining are being harnessed to augment research efforts in natural product drug development, including the design of phyto-pharmaceutical-based nanoformulations.

Databases such as PubMed, ScienceDirect, and Google Scholar contain extensive information on the use of TCM and traditional Ayurvedic medicine (TAM) for treating various ailments. The active ingredients, obtained from medicinal plants found in India, China, and Thailand, have been clinically tested by institutions such as the Central Drug Research Institute (CDRI), Regional Research Laboratories (RRL), the Central Institute of Medicinal and Aromatic Plants, and the National Botanical Research Institute (Lucknow). These tests aim to validate traditional claims, enhance product quality, and promote the sustainable use of natural resources. The following medications are included in the TAM and TCM databases, which have already been investigated through clinical studies (Table 2)

3.2 Nanotechnology applications in herbal medicine

The application of herbal medicine has experienced a transformative shift with the advancement of nanotechnology. Notably, encapsulating herbal compounds into nanostructures has emerged as a powerful strategy, significantly increasing their utility by improving stability and reducing the side effects (Anand et al., 2024). These nanocarriers are precisely engineered with controlled sizes, release profiles, and targeting moieties. These tailored properties have led to remarkable improvements in the bioavailability of traditional herbal medicines and have enhanced their targeting and penetration capabilities, marking a significant leap forward in the utilization of herbal medicine (Zhang et al., 2021b). The application of nanotechnology in herbal medicine serves various purposes (Figure 3).

A review of recent literature indicates that nanotechnology is mainly studied for two major approaches: increasing stability and enhancing the bioavailability of herbal compounds

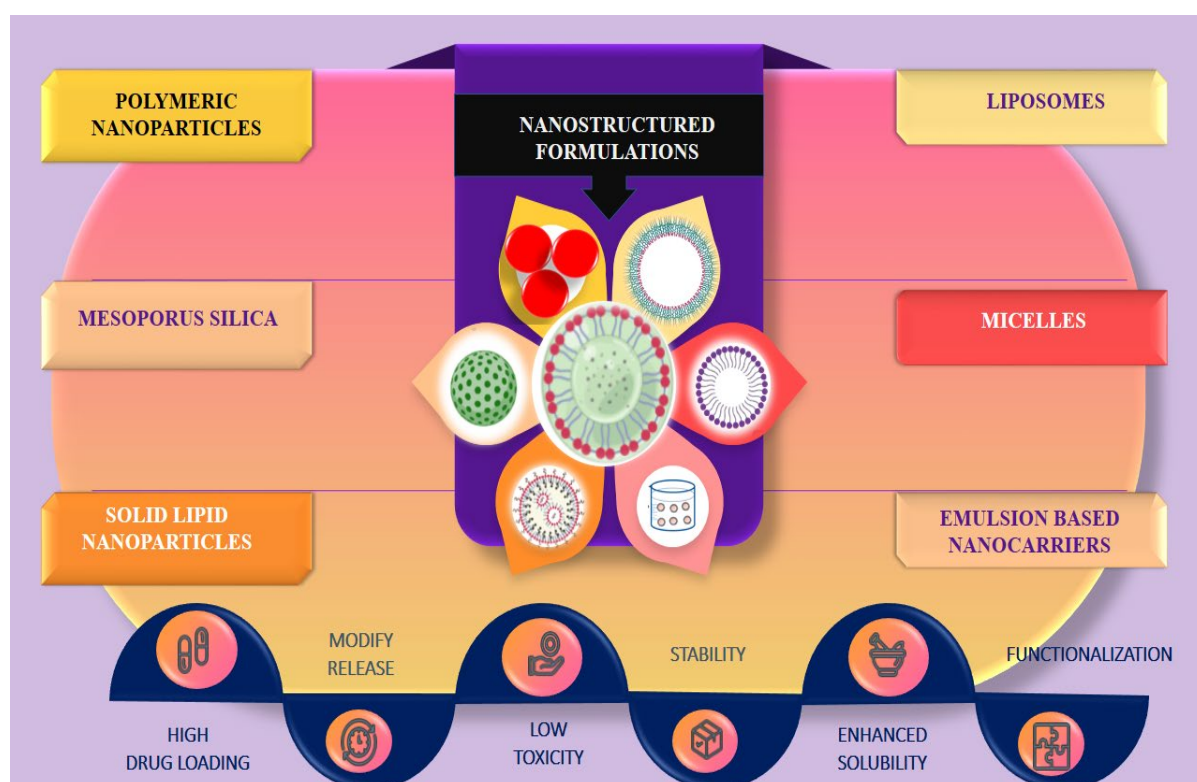
3.2.1 Increasing stability

One common application of nanotechnology is the stabilization of essential oils, which are active components obtained from herbal medicines. Essential oils offer various pharmacological activities such as anti-inflammatory, free radical scavenging, antibacterial, and cell-regenerative properties (Sakkas & Papadopoulou, 2017; Huang et al., 2019). Nanoformulation techniques, such as nano-encapsulation and nanoadsorption, have been developed to address the chemical instability and volatile nature of essential oils. Essential oils such as carvacrol, limonene, cinnamaldehyde, citronella, eugenol, thymol (Wu et al., 2019), as well as oil derived from *Artemisia arborescens* have been delivered using nanoencapsulation strategies. These include nanoemulsions (Nantararat et al., 2015; Donsi et al., 2014), liposomes (Detoni et al., 2012), solid lipid NPs (SLNs) (Valencia-Sullca et al., 2016), and nanostructured lipid carriers (NLCs) (Lai et al., 2006). These formulations are often prepared using polymers like poly(DL-lactide-co-glycolide) (PLGA) and chitosan to improve stability and achieve controlled release of the essential oils (Gomes et al., 2011; Hasheminejad et al., 2019; Maghami et al., 2019).



Table 2. Name of clinically proven botanicals used for therapeutic purpose

Derived compound/ molecule	Botanical name	Chinese name	Therapeutic use	References
Amphetamine/ Ephedrine	<i>Ephedra sinica</i>	ma huang	Antiasthmatic	(Tang et al., 2023)
Artemisinin	<i>Artemisia annua</i> L	qinghao	Anti-malarial	(Li, 2012)
Kanglaite	<i>Coix lachryma-jobi</i>	iijen	Non-small-cell lung cancer	(Normile, 2003)
Xue baoPG2	<i>Astragalus membranaceus</i>	-	Anticancer	(Ulrich-Merzenich et al., 2007)
Schisandrin C	<i>S. chinensis</i>	-	In the treatment of hepatitis B virus infection	(Luan et al., 2023)
Taxol, Paclitaxel	<i>T. Brevifolia</i>	-	Anticancer	(Wani et al., 1971; Wani & Horwitz, 2014; Holmes et al., 1991)
Apomorphine	<i>Papaver somniferum</i> L.	-	Used in Parkinson's disease	(Deleu et al., 2004)
Galantamine	<i>Galanthus woronowii</i>	-	Alzheimer disease	(Heinrich & Lee Teoh, 2004)
Nitisinone	<i>Callistemon citrinus</i>	-	Hepatorenal tyrosinemia	(Das, 2017)
Anctin-A	<i>Anrodia cinnamomea</i>	-	Anti-cancer	(Chen et al., 2019)
Crocin	<i>Crocus sativus</i>	-	treatment in major depressive disorder	(Talaie et al., 2015)
Berberine	<i>Berberis aristata</i>	-	Antidiabetic activity	(Wang et al., 2024)
Quercetin	fruits, plants, and vegetables	-	Used in chronic obstructive pulmonary disease	(Han et al., 2020)

**Figure 3.** Nanotechnology approaches herbal medicine

3.2.2 Enhancing bioavailability

Many active constituents of traditional herbal medicines, such as phenols and flavonoids, exhibit low permeability and poor solubility. However, incorporating these compounds into nanoformulations can overcome this

challenge (Gunasekaran et al., 2014). Loading these compounds into various carriers to create formulations such as NPs, liposomes, and nanocrystals can increase their bio-availability for treating various diseases, often with the aid of surfactants (Table 3).

Table 3. Examples of nanoformulations for bioavailability enhancement

Traditional herbal medicines	Nanocarriers	Disease model	References
Hesperetin	NPs Nanocrystals	Alzheimer's disease, Cancer	(Baradaran et al., 2020; Khalaj et al., 2018; Kheradmand et al., 2018)
Epigallocatechin-3-gallate	Transfersomes Nano-phytosome	Skin damage Anti-inflammation	(Avadhani et al., 2017)
Curcumin	Nanocrystals Nanogels Liposomes Polymeric NPs Mesoporous silica NPs	Anti-inflammation Cancer Central nervous system disorders	(Yavarpour-Bali et al., 2019)
Rutin	Solid-lipid NPs Polymeric NPs Lipid nano-complex Silver NPs	Hypertension Cancer Hepatoprotection	(Kumar et al., 2018; Pandey et al., 2018; Ravi et al., 2018)
Andrographolide	Nanocrystals Polymeric NPs Gold NPs	Visceral Leishmaniasis Hepatoprotection	(Das et al., 2015; Das et al., 2018; Ma et al., 2018)
Ginkgolide B	Polymeric NPs Nanocrystals	Parkinson's disease	(Liu et al., 2020; Zhao et al., 2020)
Piperine	Pro-nano lipospheres Polymeric NPs	Epilepsy	(Izgelov et al., 2018; Zhu et al., 2020)
Naringenin	Liposomes Chitosan-coated NPs	Cancer Diabetes mellitus	(Maity et al., 2017; Kumar et al., 2015)

3.3 Formulation approaches for herbal medicines

In herbal drug technology, it is essential to develop various nano-sized formulations, such as liposomes, phytosomes, solid lipid NPs, transfersomes (Figure 4), and nanoemulsions to enhance the solubility, bioavailability, and stability of active compounds (Byeon et al., 2019). This can be achieved through the development of sustained

drug delivery systems, which aim to improve pharmacological actions while minimizing toxic effects. Such an approach also helps protect the active components from chemical and physical degradation, thereby addressing key challenges associated with herbal drugs and their active components (Sarangi & Padhi, 2018; Pongnimitprasert et al., 2018; Buranatrakul et al., 2021; Sobharaksha et al., 2024).

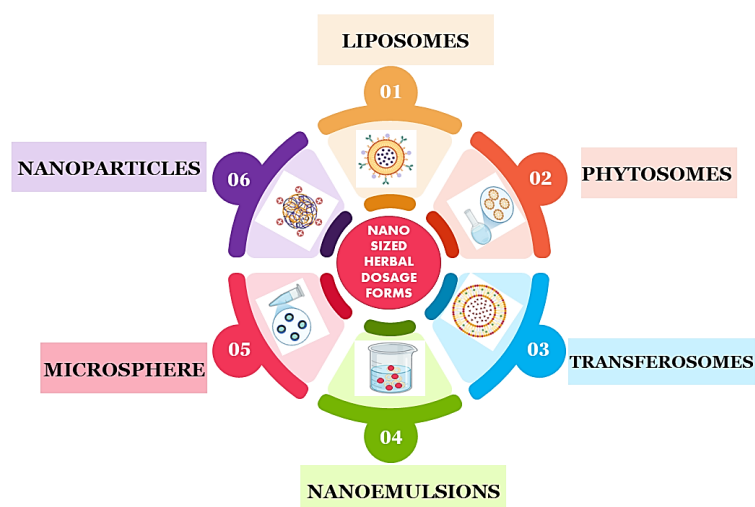


Figure 4. Different types of herbal formulations

Liposomes serve as useful carriers for delivering anti-cancer medicines, by enhancing drug accumulation at the tumor site while decreasing accumulation in normal tissues, thereby reducing the risk of toxicity (Bhokare et al., 2016). Phytosomes are lipid-compatible molecular complexes prepared by incorporating plant extracts or

water-soluble phytoconstituents into phospholipids; this approach is a key technological advance in phyto-pharmaceutical formulation and nutraceuticals (Sachan & Gupta, 2015). Other approaches to nano-formulations are compiled in Table 4.

Table 4. Applications of nanotechnology-based systems for delivering herbal extracts and active compounds

Herbal medicine	Drug delivery systems as nanotechnology	Results	References
<i>Phytolacca decandra</i> (root extract)	PLGA-encapsulated forms	Served as better chemo preventive action against lung cancer by increasing the drug's bioavailability	(Das et al., 2012)
Methanolic extract of <i>Ocimum sanctum</i>	sodium alginate chitosan NPs	Better and longer-lasting antimicrobial activity	(Rajendran et al., 2013)
Curcumin (nanocurcumin)	curcumin-loaded polymeric NPs	Freely soluble in aqueous media and increased bioavailability by blocking the activation of inflammatory mediators	(Bisht et al., 2007)
Curcumin	PLGA nanospheres	35% reduction was noted in prostate cancer	(Mukerjee & Vishwanatha, 2009)
Honokiol	Honokiol loaded polymeric NPs	Showed better results as an antitumor activity	(Zheng et al., 2010)
Coumarin isolated from (7-hydroxy-6-methoxy), an ethanolic extract of <i>Gelsemium sempervirens</i>	Polymeric nanocapsules	Better bioavailability	(Khuda-Bukhsh et al., 2010)
<i>Cuscuta chinensis</i> Lam.	<i>Cuscuta chinensis</i> NPs	Hepatoprotection and antioxidant	(Yen et al., 2008)
Quercetin	Quercetin incorporated in NPs	Antioxidant and anti-lipid peroxidation activities	(Wu et al., 2008)
Quercetin	Solid lipid NPs	Enhanced absorption in the intestine	(Li et al., 2009)
Camptothecin	Camptothecin-encapsulated NPs	Strong antitumoral activity	(Min et al., 2008)
Naringenin	Naringenin loaded NPs system	Hepatoprotective activity	(Yen et al., 2009)
Ethanolic extract of <i>Polygala senega</i>	Nanoencapsulated form	Anticancer activity	(Paul et al., 2011)
Silymarin	Silymarin hybrid liposomes	Significant hepatoprotective activity	(El-Samaligy et al., 2006)
Triptolide from <i>Tripterygium wilfordii</i> Hook	Microemulsions	highest anti-inflammatory effects	(Mei et al., 2003)
Ginkgolide B	Polymeric NPs Nanocrystals	Parkinson's disease	(Liu et al., 2024; Zhao et al., 2020)
Oleanolic acid	Micelles Nanocrystals	By increasing solubility used in Metabolic dysfunctions Cancer	(Wang et al., 2020; Markowski et al., 2022)
Liquirtin	Liposomes, Self-nanoemulsifying drug delivery system	Hypoglycemic, anti-hyperuricemic activity	(Wang et al., 2021; Wei et al., 2022)
Rutin	Solid-lipid NPs Polymeric NPs Lipid nano-complex Silver NPs	Hypertension Cancer Hepatoprotection Antithrombotic	(Negahdari et al., 2021; Shanmugam et al., 2017; Ahmad et al., 2016; Pandey et al., 2018)

New formulation approaches are opening promising avenues for enhancing the efficacy of herbal medicines while addressing the inherent challenges of using natural products in therapeutic applications (Bonifácio et al., 2014). Novel drug delivery systems—such as those offering targeted delivery, controlled release, improved stability, and increased efficiency—hold considerable potential to transform healthcare outcomes (Byeon et al., 2019). Additionally, the integration of diagnostic and therapeutic functions into a single platform represents an exciting advancement, offering more precise and effective management of diseases (Farooq, 2019). Despite these opportunities, the successful clinical translation of these innovations is hindered by several key challenges, particularly concerning the interaction of nanomaterials with biological systems and ensuring their safety and efficacy in real-world medical settings (Farooq et al., 2019b).

One of the primary obstacles is scale-up feasibility. To bring these advanced drug delivery systems to the market, production processes must be optimized for large-scale application to meet the demands of broader patient populations (Kumar et al., 2022). Another challenge lies in the development of multifunctional nanotechnology-based systems that satisfy various biological and therapeutic criteria. Targeting efficiency also remains a significant issue, as NPs must accurately deliver therapeutic agents to specific sites within the body. This stage of development is often constrained by limited budgets and the need for extensive trials.

Safety concerns related to toxicology and biocompatibility are crucial for gaining clinical acceptance. These nanocarriers must meet stringent international standards to advance to in clinical trials. Furthermore, research on nanomedicine using natural products is still in its infancy and is often confined to laboratory settings. The high manufacturing costs associated with nanosystems for herbal medicines contribute to elevated prices, limiting widespread adoption (Bosetti, 2015). More extensive research is required to evaluate mechanisms of action and define regulatory frameworks.

The complexity of traditional herbal prescriptions—often comprising multiple active components—further complicates efforts to study their therapeutic effects in a systematic manner. Additionally, regulatory hurdles pose a significant barrier, especially when compared to Western nanomedicines that have already received FDA approval. Establishing standardized clinical trials and comprehensive evaluations is essential before these innovative therapies can be commercialized on a broader scale (Sookying et al., 2021; Teja et al., 2022).

Despite these challenges, the convergence of nanotechnology with natural products holds great promise for advancing disease treatment, including cancer therapies. As scientific understanding deepens and technological barriers are addressed, the integration of nanomedicine and herbal compounds could pave the way for a new era of healthcare innovation.

4. STANDARDIZATION AND QUALITY CONTROL OF HERBAL PRODUCTS

Herbal products are gaining popularity due to their perceived safety and efficacy in healthcare. However, their broad acceptance is hindered by the lack of a predefined quality control profile, unlike conventional medicines. Notably,

regulatory bodies such as the Ministry of AYUSH in India and the WHO at the global level have initiated efforts to establish standards for herbal products to ensure consistent efficacy and safety. Herbs contain complex chemical constituents responsible for their therapeutic effects (Bandaranayake, 2006). The quality and quantity of these constituents depend on varying factors such as geographical origin, harvesting, processing, methods of preparation, and correct species identification. Hence, the quality control of herbs is based on establishing the identity, purity, and assay of the active compounds (Ahmad et al., 2006). This process involves the standardization of botanicals. Standardization of herbs ensures that an herbal preparation contains a defined phytoactive content. This process involves all aspects of manufacturing, quality control, and quantifying active ingredients to ensure the desired therapeutic outcome at a specific dose (Madhav et al., 2011; World Health Organization, 1994).

To ensure the consistency of herbal products, chemical profiles of herbal products are developed and compared with clinically proven reference substances. This approach of “phytoequivalence” was developed in Germany to ensure the consistent quality of herbal medicines (Liang et al., 2004). The WHO has published various technical guidance documents related to the quality and safety of herbal medicines. These include “Quality control methods for herbal materials” (2011), “Guidelines on good agricultural and collection practices (GACP)” (2003), and “WHO guidelines for assessing the quality of herbal medicines with reference to contaminants and residues” (2007). (World Health Organization, 2003, 2007, 2011). China, Japan, and the European Union have also developed their own guidelines for medicinal plants to ensure safe products free from harmful substances. To ensure effective quality control of herbal products, it is advisable to systematically analyze and document the scope and content of herbal monographs included in pharmacopeias from different countries. Such an analysis would offer a comprehensive view of current standards and support efforts toward harmonizing quality benchmarks globally. For herbal dosage forms, pharmaceutical parameters are additionally required to be evaluated (Ong, 2004). The CMC (chemistry, manufacturing, and control) requirements for botanicals are different from those for synthetic drugs. In the United States, it is not necessary for the producer of a botanical to identify the active constituent at the IND (investigational new drug) stage. The quality evaluation parameters of herbal products are depicted in Figure 5.

4.1 Role of regulatory authorities

Herbal products are regulated internationally under various classifications, including supplements, complementary medicines, natural health products, medicines, prescription medicines, and traditional herbal medicines (Sharma, 2015).

In India, they are regulated under the Drug and Cosmetic Act, 1940, in which regulations for Ayurveda, Unani, and Siddha medicines are set. This act controls the licensing, manufacturing, quality control, and export of herbal medicines. Pharmacopoeias and formularies are also available for the quality standards of these medicines. In the United States, botanicals are classified as drugs, foods, or dietary supplements by the FDA. It regulates dietary substances under the Dietary Supplement Health



and Education Act of 1944. The manufacturing of dietary supplements must adhere to CGMP for dietary supplements. For the European Union, the EMA (European Medicines Agency) provides two types of registration for herbal medicines. One is a full marketing authorization, where the entire dossier, including information on quality, is submitted under Directive 2001/83/EC. The other category is for traditional herbal medicinal products that do not require medical supervision. If these products have sufficient evidence of long-term traditional uses, but lack the extensive

scientific literature required for full authorization, they can undergo a simplified registration procedure under Directive 2004/24/EC (Bilia & do Céu Costa, 2021). Apart from this, many countries with a trend toward using herbal medicines have laid down their own quality and regulatory guidelines to follow. However, developing globally accepted herbal products requires global harmonization and standards to maintain product consistency.

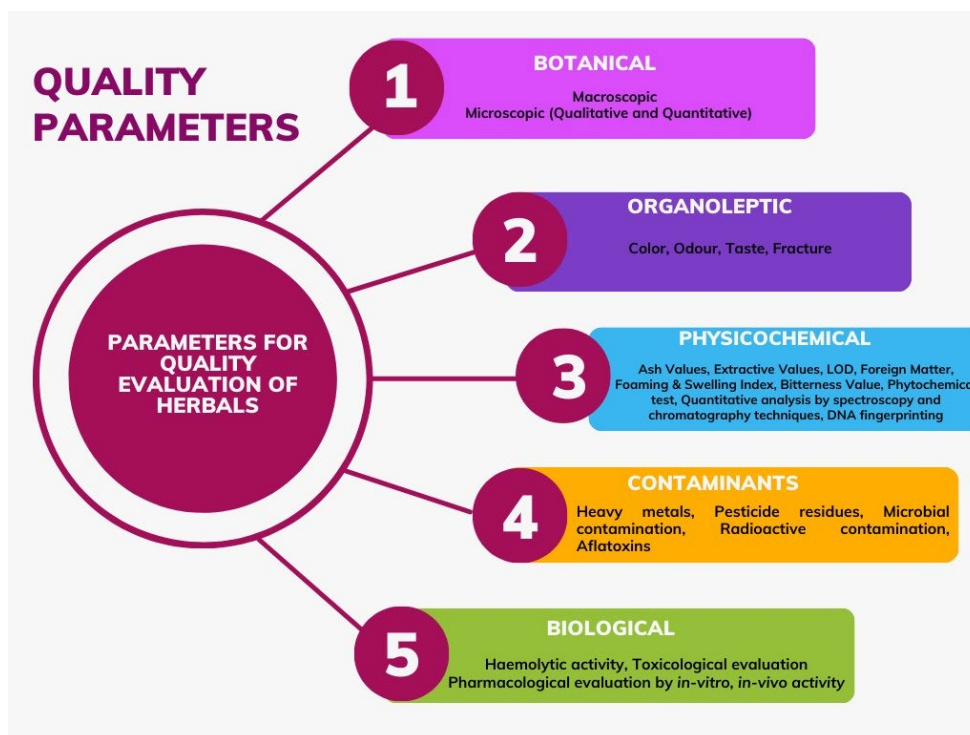


Figure 5. Quality evaluation parameters for herbal products

4.2 Analytical techniques for quality assessment

Quality assessment of herbal products is very important to ensure the safety and efficacy of herbal drugs and formulations. It comprises qualitative and quantitative analysis of phytoactives present in herbs along with the detection of any contaminants (Ahmad et al., 2006). Efforts are also being made to explore the chemical profiles of herbs, which have not been explored before. Generally, the quality control of herbal drugs and formulations comprises analytical evaluation with different chromatographic and spectroscopic techniques (Klein-Junior et al., 2021).

Chromatography methods separate the complex mixture of actives based on the stationary and mobile phases and characterize the separated constituents. Paper and thin-layer chromatography (TLC) are mostly employed for qualitative identifications where detection can be achieved under ultraviolet light, visible light, or by spraying with a specific reagent (Boland et al., 2007; Thipunkaew et al., 2024). High-performance thin-layer chromatography (HPTLC) uses percolated stationary plates with high-end instrumentation to produce clear resolution and high reproducibility. The Ayurvedic Pharmacopoeia and many other pharmacopoeias utilize HPTLC as a reference method for the quality evaluation of herbal products.

HPTLC fingerprinting, marker compound identification, and the assay of actives in crude drugs and herbal formulations can be performed using HPTLC (Do et al., 2019; Tomar et al., 2019). Gas chromatography (GC) is widely used for the analysis of volatile constituents present in plants and is now often coupled with mass spectrometry for the profiling of these volatile constituents (Ansorena et al., 2001). High-performance liquid chromatography (HPLC) is employed widely nowadays for herbal drugs, providing high sensitivity in detection, and is also coupled with mass spectrometry (LC-MS), for herbal drug analysis (El-Aneel et al., 2009).

In spectroscopy, ultraviolet (UV), infrared (IR), Fourier transform IR (FT-IR), nuclear magnetic resonance (NMR), and atomic absorption spectroscopy techniques are used for the quality control of herbal products. FT-IR and NMR are helpful to differentiate related plant species and are used to explore or authenticate plants (Krishnan et al., 2005; El-Aneel et al., 2009). Atomic absorption spectroscopy and its upgraded version, inductively coupled plasma atomic emission spectroscopy, are employed for heavy metal and macro-micronutrient analysis of plants. Hyphenated spectroscopy and chromatography techniques like LC-MS, ICP-MS, and GC-MS have played a pivotal role

in the authentication, quality evaluation, and standardization of botanicals (Nikam et al., 2012).

For herbal medicines, the extraction methods and sample preparation are very important to obtain well-resolved fingerprints due to the presence of multiple constituents. This is even more critical when multiple herbs are included in a single preparation. The chromatographic fingerprints produced by instruments are highly valued because they represent various chemical constituents present (Kamboj, 2012). In cases where phytochemical analysis cannot distinguish between an authentic drug and an adulterant, DNA analysis has emerged as a key tool for herbal standardization. The technique of DNA fingerprinting is now widely used to determine plant provenance and for the genotypic characterization of species (Shaw et al., 2009). Plant metabolomics involves the qualitative and quantitative identification of herbal medicine metabolites, which play an important role in the execution of therapeutic effects. The technique is applied for the identification of phytoactives in herbal products (Hong et al., 2016). Recently, metabolomics has been used to determine the efficacy and toxicity profiles of herbal medicines (Xiao et al., 2022).

4.3 Good manufacturing practices (GMP) for herbal medicines

GMPs are guidance documents issued by international organizations for pharmaceutical industries and national regulatory authorities in different countries to ensure high standards of quality, efficacy, and safety in any manufacturing process for health products (Gouveia et al., 2015). Given the worldwide demand for herbal drugs, it has become crucial to maintain GMP to achieve the desired quality of products (Mukherjee, 2002). The WHO, at the international level, has provided guidelines for the manufacture of herbal medicines (World Health Organization, 2007). Quality assurance, GMP, personnel, premises, materials, equipment, documentation, production, and quality control are mentioned in the guidelines. Based on that, different countries have drafted their own guidelines of GMP for herbal medicines. In India, according to the Drug and Cosmetic Act, 1940, Schedule T describes GMP for Ayurvedic, Siddha, and Unani medicines. GMPs are directed by national regulations, which vary based on how these products are defined. For example, they are called “traditional medicines” European Union and India, “natural health products” in Canada, and “dietary supplements or botanical drugs” in the United States (Devi et al., 2022).

5. CONCLUSION

The combination of herbal medicine and nanotechnology is an essential tool for advancing herbal medicine research, offering enhanced bioavailability and the potential for the treatment of various chronic diseases, such as cancer and cirrhosis, with reduced toxicity. Herbal treatments based on nanotechnology have enormous potential, despite the challenges associated with ensuring their safety and effective use. The integration of traditional herbal medicines with contemporary drug delivery systems, including nanotechnology, has emerged as a promising avenue for pharmaceutical advancements. The active ingredients in these medicines are responsible for

producing the desired therapeutic effect. Integrative therapies such as traditional Tibetan medicine (TTM), traditional Chinese medicine (TCM), and traditional Indian medicine (TIM) are highly regarded for the treatment of many diseases and have gained widespread international acceptance due to the use of advanced diagnostic technologies. This combined approach has the potential to provide novel therapeutic solutions that may significantly improve public health in the foreseeable future. The use of nanocarriers for natural products and herbal treatments is expected to become an important part of modern drug delivery, enhancing the efficacy and value of these traditional remedies. The establishment of standards and monographs for herbal products can help address the efficacy and safety issues. Overall, herbal nanomedicines show great potential to be safer, have higher bioavailability, and offer enhanced therapeutic value compared to conventional herbal preparations and some synthetic drugs. One of the main lacunae is the lack of coordinated, multi-disciplinary studies to rigorously establish their clinical efficacy. This aspect should be the focus of future research endeavors.

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