ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 12, 2022

Online - 2455-3891
Print - 0974-2441

Review Article

CURRENT STATUS AND CHALLENGES OF HERBAL DRUG DEVELOPMENT AND REGULATORY ASPECT: A GLOBAL PERSPECTIVE

CHOWDHURY MOBASWAR HOSSAIN[1]*, MEETA GERA[2], KAZI ASRAF ALI[1]

[1]Department of Pharmaceutical Technology, Maulana Abul Kalam Azad University of Technology, Nadia, West Bengal, India. [2]Department of Biochemical Engineering and Biotechnology, Indian Institute of Technology, New Delhi, India. Email: drcmhossain@gmail.com

Received: 14 August 2022, Revised and Accepted: 22 September 2022

ABSTRACT

Conventional herbal medication has picked up a gigantic sum of intrigue around the world due to its viability in the treatment of extreme illnesses from the period of antiquated civilizations. Phytomedicines are considered a major health-care supplier around the globe, especially in rustic and farther ranges. A huge segment of individuals depends on or accept home-grown drugs as an essential cure for different afflictions rather than manufactured drugs. Researchers are paying much attention to herbal medicine as compared to synthetic drugs due to their severe side effects, and toxicity with less efficacy and specificity. Despite the significant increase in global interest in the investigation and development of new botanical products, only a few have been approved till now. Natural product medication development has significant technical and monetary hurdles, including a time-consuming formulation process, quality assurance, safety, therapeutic efficacy, promotion, and administrative issues. To meet these challenges, the regulatory agencies EMEA, ICH, AYUSH, DCGI, WHO, and U.S. FDA trying to bring these herbal drugs under the regulatory pipeline under the NDA approval process. Moreover, the process of drug discovery has also been revolutionized with the new advent of technologies such as the successful drug development of a novel therapeutic agent is critically relying on the process which adopts novel approaches and involves the concept of ADMET (i.e., absorption, distribution, metabolism, excretion, and toxicity) in the early stages of drug discovery along with the interaction profiles of herb-herb and herb-synthetic. In the present review, we will address the noteworthy opportunities and issues related to phyto-drug improvement in various developing and developed nations such as Europe, U.S. and India, its commercialization with regulatory guidelines, and recommended potential methods to bring them up into the mainstream of modern medical practices and healthcare.

Keywords: Herbal medicine, Challenges, Regulatory guidelines, Monetary hurdles, Government schemes.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i12.46134. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

In the 21st century, pharmaceutical sciences have made tremendous progress throughout the world. Overall lethality rates have reduced, life expectancy has improved, numerous new life-saving pharmaceuticals have been discovered to aid in the fight against a variety of infectious and other diseases, and technological advancements have increased modern science's potential [1]. Plants include a variety of molecular entities with varying levels of bioactivity, which have traditionally been utilized to develop novel medications and new leads for drug development against a variety of diseases [2]. Concurring to the World Health Organization (WHO), almost 80% of individuals still utilize herbal medicines for essential well-being care, and ethno pharmacological origins account for 80% of 122 plant-derived pharmaceuticals [3]. Herbal medications are exceptionally vital, have lesser side effects, and are congruous with our biological system; however, these are not broadly considered today's engineered drugs. The pharmaceutical sector is one of the world's most important industries for economic growth. The entire revenue market for herbal pharmaceuticals is 50.9 billion dollars, which is much smaller than the manufactured drug market, which was 934.8 billion dollars in 2017 [4]. Herbal exports include Ayurveda, Unani, Siddha, and homeopathy (AYUSH) medications, which account for 3% of total Indian pharmaceutical exports. Raw materials account for 70% of the herbal sector's exports, which are expected to be worth Rs. 10 billion per year. Finished items, such as herbal extracts, account for 30% of the export. India's contribution to the worldwide herbal export market, however, is <1%. Even though AYUSH is one of India's oldest traditional systems of treatment, it has been unable to capitalize on the expanding market's prospects [5]. According to reports, around 8000 herbal species are utilized as ethnomedicine, and ethnic communities have devised 25000 formulations that must be identified, verified, and documented [6]. The pharmaceutical industry has shown less attention for developing herbal medicines due to the complex process of drug development, quality control, security, adequacy, promotion, and administrative guidelines, and medical people are also not interested much in it [7]. For low-income and developing countries, this scenario becomes a financial burden. In this review, we have highlighted the prospects and problems related to plant-derived drug development and its commercialization, as well as the future breadth of research possibilities.

THE STATE OF THE ART OF HERBAL MEDICINE

Ayurveda, Unani, and Chinese medicine, as well as homeopathy and naturopathy, are all plant-based systems of medicine. These medical techniques, however, were neglected and even proclaimed illegal by authorities throughout the colonial era since they were considered archaic and unscientific. When chemical analysis became possible in the early nineteenth century, scientists began extracting and manipulating the strong medicinal chemicals inherent in plants to use them as ingredients in allopathic remedies [8]. Chemists began synthesizing these chemicals and generating their own plant-based molecules later. In 25% of allopathic prescription medications, at least one active component originated from plants can be found [9]. According to recent studies, herbal remedies have been shown to be as effective as conventional pharmaceuticals while also being relatively safe [10]. The plant produces antimicrobial peptides to protect them, and these peptides appear to have a lot of clinical utility. Antimicrobial peptides have a high selectivity for prokaryotes and minimize the probability of microbial resistance [11]. Self-assembling peptide nanofibers may prove to be an efficient SARS-CoV-2 vaccine, according to current Corona vaccine engineering research [12]. Herbal medicine research has also benefited from genomics research. Because genomics can uncover important gene clusters and gene duplication events for specialized metabolism, it could aid in the discovery of gene-metabolite connections in plants. Gene activity in medicinal plants must be

thoroughly examined by genome sequencing, assembly, and annotation because the bulk of many new plant-derived compounds is secondary metabolites such as terpenoids, alkaloids, and phenolic compounds. Hence, there have only been a few well-assembled herbal genomes revealed. To predict secondary metabolite pathways in medicinal plants, genomic data can be integrated with the proteome, transcriptome, and metabolomic data [13].

HERBAL MEDICINE AND ITS IMPORTANCE

Plant-derived medicinal active constituents have earned a reputation as "people's drugs" as they are easily available, claimed safe and secure, easy to prepare methods, and are gradually displacing standard restorative treatment frameworks in numerous nations as improvements in quality control and clinical researches way public opinion in their support.

Because of the negative effects of contemporary medications, the inability of existing therapies to address chronic conditions, and germ resistance, herbal products have seen a huge resurgence in popularity in recent years. Herbs or herbal products are utilized by a vast number of people for basic healthcare requirements, according to the WHO. Herbs, herbal materials (such as plant parts), herbal preparations, processed and finished herbal products, and active ingredients make up herbal medicine [13]. Traditional herbal remedies are utilized by 80% of the population in numerous Asian and African countries for primary healthcare, but complementary and alternative medicines (CAMs) that mostly consist of herbal items are used by 70–80% of the population in many rich countries. "Kampo" medications are prescribed by 60–70% of allopathic doctors in Japan (largely composed of herbal products). Plant-based medications are prescribed by over 70% of German doctors. Natural resources contribute to more than 70% of modern pharmaceuticals in India, and several synthetic equivalents have been generated from prototype compounds derived from plants. According to statistics, natural materials are used in more than 60% of cancer treatments on the market or in research. Plants are currently used to make around 80% of antibacterial, immunosuppressive, cardiovascular, and anticancer drugs. Over 70% of the 177 anticancer drugs approved are based on natural or mimetic chemicals [14]. According to the WHO, Regional Office for the Americas, herbal medicine is used by 71% and 40% of the populations in Chile and Colombia, respectively. In Australia, France, and Canada, CAM is predicted to be used by 46%, 49%, and 70% of the populace, respectively. Natural or herbal medicine is used by around 158 million Americans [15]. Plants are always the primary source of medicine or treatment method in several ancient medicinal systems.

PHYTOCHEMICALS, SECONDARY METABOLITES, AND ACTIVE MOLECULES AND THEIR BIOLOGICAL ACTIVITIES

Biological activity refers to a drug's or bio-chemical's substantial or side effect on living things. The sections are influenced by the amount of medication used. The biological activities of phytochemicals, which are derived from plants, have shown many potential biological activities against several diseases and illnesses and are highly effective [16]. Only 15% of the world's estimated 250–400 thousand plant species have been researched phytochemically, and only 6% have been screened systematically for biological activity, according to estimates [12]. More than 60% of clinically utilized medications contain natural chemicals or their derivatives, and more than 120 chemical moieties originating from plants are used as drugs against life-threatening diseases [17].

PHYTO DRUG APPLICATION LANDSCAPE: OUR REGULATORY STATUS TO DATE

Botanicals and other natural materials have been used as herbal medicines to cure a wide spectrum of human ailments for thousands of years. Several constituents may contribute to the overall therapeutic benefit of botanicals because they are naturally heterogeneous combinations with few distinct active constituents. Due to the inherent chemical complexity of botanical blends, botanical drug researchers confront arrange of obstacles when commencing an investigational new drug (IND) clinical study, such as assuring consistent product quality [3]. Many regulatory scientists throughout the world are becoming more aware of cases of clinically significant hepatotoxicity linked to several herbal and botanical products advertised as dietary supplements [18]. Concerns regarding this adverse effect have grown in the United States (US) as the usage of dietary supplements has progressively increased among demographically different groups of customers over the last few decades [3]. An ongoing prospective multi-center analysis financed by the National Institutes of Health (NIH) has revealed that dietary supplements and herbal products were causally linked to15.5% of domestic hepatotoxic episodes leading to inclusion, underlining this problem [19]. Companies or scientists in the US gain clearance to begin clinical trials by submitting an IND. Food and Drug Administration (FDA) urges companies to contact the agency before submitting an IND since an early engagement with FDA officials can help to avoid clinical hold (FDA refusal to allow research to proceed) concerns. A pre-IND meeting is one type of communication that can offer sponsors information that will help them prepare to submit a complete IND. The NDA process is used to regulate, and control marketed new medications. The medication sponsors use the NDA application to ask the FDA to approve a new medicine for sale and marketing in the US. The NDA incorporates the information gathered during animal studies and human clinical trials, which are generally conducted under an IND (FDA, 2019). Botanical medicine products are regulated in the same way as small-molecule pharmaceuticals and follow the same path. The FDA established the Botanical Review Team (BRT) in 2003 to conduct a pharmacognosy analysis of all botanical submissions, which includes an examination of botanical raw materials, previous human experience, and the phytochemical ingredient profile for all original IND and NDA submissions. From 1984 (when botanical INDs were first received) until the present, the FDA BRT has an in-house database of botanical pre-IND, IND, and NDA submissions [3] (FDA, 2019). Various regulatory agencies have differed in their requirements for toxicological evidence, as well as how they used clinical trial data, adverse event records, and the historical use of botanicals as medicines and foods in their reviews. As a result, it is important to think about how each product is classified based on the jurisdiction in which it is created and sold. Even if a product is categorized as being in the same category, regulatory requirements in different nations may differ. For items that are "Classified as Medicines," regulations are usually consistent across jurisdictions. The regulatory criteria for "Classified as Supplements" items, on the other hand, vary widely between countries. Despite significant differences in regulatory standards among jurisdictions, one thing that all counties have in common is that consumer safety is the primary concern [17].

MARKET VALUE OF HERBAL DRUGS

Plant-derived medications have produced an impact on people all around the world because of their health benefits, as well as the fact that they are less expensive in many countries than modern synthetic treatments. Increased consumer knowledge, FDA rules for current Good Manufacturing Practices (GMP), the high cost of contemporary pharmaceuticals, and few or no adverse effects are market-driven dynamics that have expanded the global market for herbal medicines. The world's largest producers of herbal medicinal plants are China and India. Most of the herbal medicines are produced in France, followed by Germany in Europe [20]. Saudi Arabia and the United Arab Emirates are the world leaders in the manufacture of herbal medicines in the Middle East. Africa continues to lag behind the rest of the world in herbal medicine manufacturing due to its weak economic and turbulent political status. According to estimates, the global market for herbal medicine will reach $5 trillion in 2050, up from $60 billion in 2010 [21].

The global herbal pharmaceutical companies leading in this sector and growing rapidly include Nutraceutical International, USA, Shen Chang Pharmaceutical Company, China, Himalaya Drug Company, India, Zandu Pharma, India, Dabur, India, Hamdard Laboratories, India [22]. Large

pharmaceutical corporations and minor pharmaceutical businesses dominate the worldwide herbal market, resulting in a highly competitive and fragmented sector. In terms of product portfolios, quality, and pricing, multinational firms are expanding their operations into emerging countries, placing pressure on regional and indigenous herbal companies. There is a lot of competition, and it is just going to grow worse. Large organizations are focusing on extraction procedures and purification protocols to provide the high-quality product required to expand the market of herbal medicine. Some limitations are there, such as unstable regulations and authority in terms of quality control and patent laws, and a lack of high-quality research data for the expansion of the herbal industry [23].

PROBLEMS AND CHALLENGES FACINGIN HERBAL DRUG DEVELOPMENT AND THEIR PROMOTION

Due to their natural origins and lower side effects or unhappiness with the results of synthetic pharmaceuticals, herbal medicines, and their preparations have been widely utilized in developing and developed countries for thousands of years. Oriental herbal medicine has several distinct qualities. All herbal remedies, whether presented as single herbs or as a combination of plants, are referred to as medicine preparations [24]. Medicinal ingredients are used in traditional remedies. Plants, minerals, organic matter, and so on are all examples of organic matter. Herbal remedies are mostly those that are used in traditional medicine which primarily treats patients with medicinal plant mixtures [25]. These medications are made of eco-friendly procedures, renewable raw material resources will be available, bringing economic benefits. The people who grow these basic materials should profit [26]. Due to the availability of thousands of medicinal plants in various bioclimatic zones, India is regarded as the "Emporium of Medicinal Plants" [27]. Both in modern medicine and in traditional medicine, medicinal plants continue to deliver essential therapeutic substances. The examination of the efficacy of plant-based pharmaceuticals used in traditional medicine is being focused on since they are inexpensive, have few side effects, and as reported by the WHO, approximately 80% of the population of the world generally depends on herbal medicines [28].

FORMULATION DEVELOPMENT

The advancement of herbal medicine within the scaffold of evidence-based medicine is comparatively the latest. Applying the techniques of western-based pharmaceuticals to herbal medicines shows the research workers a multifaceted set of challenges. On the other hand, it is important that research plans in herbal drugs and conduct be systematically and strong, whereas on the view of medical philosophies and practices that escorts the use of conventional herbal medicines [29].

STABILITY OF HERBAL DRUG

Stability testing aids in the establishment of storage conditions for a drug product's Quality-Safety-Environment (QSE) to be maintained during its shelf life. However, confirming QSE for an herbal product under the effect of diverse storage circumstances is far more difficult than it is for a synthetic drug product. There are some hurdles that make the stability testing of herbal drugs difficult, are chemical complexity, variety in biochemical properties of raw material, choice of marker(s) for stability testing, and influence of enzymes present in herbal products [30].

INSUFFICIENT PHARMACOKINETIC INFORMATION ON HERBAL DRUGS

The amount of a drug that reached systemic circulation and the location of action are tied to the dose, the route of administration, and the pharmacokinetic properties of drugs. Data on the dose and administration route utilized to achieve therapeutic results without adverse reactions are included in preclinical and clinical studies that were conducted to determine a new drug's approval rating. Furthermore, the pharmacokinetic data collected in the above studies, combined with the assessment of the drug's long-term safety and efficacy (benefit-risk ratio), reveal a few factors, including disease states, age, genetic polymorphisms, and poly pharmacy, that may alter the drug's pharmacokinetics and thus influence its responses. However, the use of a medicinal plant concurrently with medicine may result in a lack of therapeutic benefit or unforeseen negative side effects [31].

EFFICACY, BIOAVAILABILITY, SAFETY, AND TOXICITY OF HERBAL PRODUCTS REGULATION

Herbal medications are regulated and registered differently in different countries. Herbal medications are classified into prescription and non-prescription medicines in the countries where they are controlled. Other than medicinal use, herbal products can also be grouped in various ways. Furthermore, the regulatory status of a few herbal drugs may vary from country to country. The concerned competent providers and distributors of specific chemicals are normally included in the national regulatory framework. As a result, the regulatory status of these products dictates who has access to them and how they are distributed.

QUALITY ASSURANCE AND CONTROL

Every country that regulates herbal medicines should have quality control and quality assurance in place, such as national quality specifications and standards for herbal products, GMP for herbal drugs, labeling, manufacturing license, imports, and merchandise.

PHARMACOPOEIAS

Quality specifications and standards for various types of herbal materials, such as volatile oils and powdered herbal products, are defined by national and regional Pharmacopoeias. Herbal materials are used and included in such Pharmacopoeias are dependent on the items' local availability.

ACTION REQUIRED

Herbal medicines, like other human medications, should be controlled by a drug regulatory procedure to make sure that they meet the necessary criteria of safety, efficacy, and quality [32-34].

CHALLENGES IN CLINICAL TRIALS AND ETHICS WITH HERBAL DRUGS

Herbal medications contain various chemical constituents (phyto-constituents) that have been utilized for ages and are recognized for their pharmacological effects on the body. Herbal medications are widely accepted and used over the world, implying their safety and efficacy. However, most herbal medicinal products have insufficient pharmacokinetic, pharmacological, and clinical data, which contributes to the lack of guarantee of safety and efficacy. The problem of herbal drug regulation is exacerbated by the large gap in satisfying statutory criteria for research on herbal medications [35]. There is not enough scientific evidence to assess herbal medications' safety and efficacy. The trial drug's quality must be checked for batch-to-batch consistency of the active ingredients. It is tough to create active and control groups that are similar in color, smell, and taste to the herbal medication, which can't be replicated when made a placebo. These difficulties can be mitigated or eliminated by using the most up-to-date clinical research procedures and protocols. Because quality control of herbal medicines is complex and demanding, relevant and adequate standards for the assessment of safety and efficacy for various categories of herbal medicines should be defined to save money and time. Furthermore, attempts should be made to include conventional medicine in national medical practices [36]. The clinical research can begin only after collecting necessary preclinical data on the intervention and receiving proper clearance from the relevant Health Authority/Ethics Committee for the study's design and objectives [37]. The different hurdles and regulatory rules highlighted for herbal medication clinical trials will be important for many sectors to consider before proceeding with a clinical study of their product.

Herbal drug research is fraught with difficulties that must be overcome. Before registering an investigational new medicine for performing big phase III studies, they include difficulties such as financial, ethical, product standardization (quality control), study design, and regulatory requirements. The WHO established operational recommendations in 2005 covering regulatory criteria for herbal product clinical studies [38].

The success of traditional herbal treatments is primarily determined by the patient's participation [39]. Traditional medicine makes extensive use of placebo effects in offering psychological support to patients in addition to physical therapies to optimize them on specific factors that contribute to the effectiveness of any therapy. Herbal medicine treatments are complicated, involving a combination of active ingredients as well as administration guidelines [40]. As a result, the patient's willingness, and drive to continue the therapy determines the efficacy of the herbal treatment. However, using blinding and randomization [41], these variables can be reduced.

The selection of controls is another challenge in randomized clinical trials of herbal medications. Controls are chosen obeys like the intervention group as possible, as comparator comparability is required if the study is to give evidence of a particular impact of the herbal medication [42]. The parameters such as color, odor, length, frequency of intake, the believability of the therapy to the patient, and physical circumstances in which treatments are provided should all be regulated [43]. Selecting a matching control for many crude drugs, for example, ginger having a distinct odor, is a difficult challenge [44]. In this part, we will be focusing on the problems of herbal medicine clinical research as well as herbal medicine regulatory concerns.

QUALITY CONTROL-RELATED ISSUES

Several suggestions for quality monitoring and cultivation of raw materials for herbal formulations were made during a WHO conference in 2000. The development of a good agricultural and collection Practices (GACP) subcommittee to facilitate the availability of high-quality herbal medicines on the market by providing training and support to small producers and farmers was one of the proposals. Incentives for cultivators of herbal phyto-constituents might be offered to encourage GACP implementation. These services include offering technical and logistical assistance in identifying optimal agricultural production areas, delivering seeds and seedlings, selecting fertilizers and pesticides, and providing or providing advice on harvesting and primary processing gear [34].

Quality control maintains the quality of goods by adhering to well-structured and defined requirements. Official pharmacopoeias, monographs, handbooks, and other sources of standard parameter information are available [45]. Various analytical techniques may be employed to find out the quality of herbal materials. The validity, precision, accuracy, and resilience of the approach must all be considered while selecting analytical methods. It is now feasible to identify and quantify the test chemical using advanced methods such as gas chromatography (GC), high-performance liquid chromatography (HPLC), and gas chromatography-mass spectrometry (GC-MS) [33].

ADMINISTRATIVE ISSUES

This creates significant difficulties in defining the idea of national regulation of herbal materials, while also confounding patients and customers [32]. Since 1994, natural products are regulated in the US under the Dietary Supplement Health and Education Act (DSHEA) [46]. A nutritional supplement is defined as an edible material that has a "dietary element" and is meant to augment the diet. Herbs, minerals, vitamins, and other botanicals are among the nutritional constituents of these products [47]. Further toxicity studies are typically not necessary under the DSHEA for the herbs available in the market before 1994 (NIH Office of Dietary Supplements, 2011) [48]. In this case, the FDA is responsible for proving that an herbal therapeutic product or "dietary component" is harmful or unfit for human consumption. In many developing countries like India, another key difficulty is the exchange of regulatory information on herbal medications between regulatory agencies and safety monitoring or pharmacovigilance centers [32].

PHARMACOVIGILANCE

The enormous worldwide usage of herbal items and pharmaceuticals is a past instance for them to be incorporated into pharmacovigilance systems. In respect of population experience, it is vital to identify the hazards involved with the usage of herbal medicine and the safety of the herbal materials that have become a major public health concern in this respect. The requirement for pharmacovigilance for the interaction between drugs and herbal products is critical for identifying and assessing hazards associated with the use of herbal items (safety, efficacy, and superiority), which are not usually rigorously researched and are frequently not subject to regulatory approval [49]. Herbal product pharmacovigilance centers are mandated to examine and gather information about the safety and efficacy of herbal medicines by analyzing the side effects of drugs. There is no question that the recent increase in poisoning incidents of the use of herbal drugs in many parts of the world necessitates the need for extensive toxicity evaluation as well as pharmacovigilance on herbal medicines to encourage their appropriate application and safeguard human wellness [50].

IPR AND BIOPIRACY

Biopiracy is a major hindrance to the spread of herbal traditional medicine. Conservation of traditional knowledge is so critical for our development [13].

IRRATIONAL USE

Herbal products are commonly considered to have no side effects or interactions; however, this is not the case. As a result, irrational use of these medications can lead to a variety of issues that might stymie their development [51]. In this situation, when traditional medicine and knowledge are on the verge of extinction, it is imperative that we moves wiftly and decisively to conserve and preserve our history.

Regulatory agencies now have the responsibility of monitoring the regulated and quality flow of herbal products and facilitating their development to clinical trial phases. If regulatory agencies collaborate closely with academic institutions, research institutes, research clinics and centers, hospitals, industry, and pharmacy colleges, the aim will be achieved sooner rather than later.

QUALITY CONTROL OF HERBAL DRUGS

Herbal medical goods are those that are derived from plant resources for human treatment and well-being. It is critical that the quality of herbal medicines be monitored in the same way that chemically manufactured medications are. However, as compared to synthetic pharmaceuticals, the regulatory standards for herbals are less stringent. This is causing a drop in the quality of herbal goods due to deliberate and inadvertent adulteration, drug substitution, etc. As an alternative, it has dangerous consequences for customers' health. Hence, it is difficult to control the standards of the quality of herbal drugs for the improvement of human health.

Optimization and phytochemical research are done; in addition, numerous quality control instruments are utilized to ensure the quality of herbals. For quality assurance, both qualitative and quantitative metrics are necessary. The analytical techniques utilized for the quality control of herbal drugs are ultra-violet spectroscopy, HPLC, liquid chromatography coupled with mass spectroscopy (LC-MS), thin-layer chromatography, high-performance thin-layer chromatography, etc.

The quality monitoring and maintenance of the quality of herbal materials are very much important. The pharmacopoeial features of quality control include product identification, adulterants, and

substituent, purity, and the assay of the pharmaceutical constituents. Standardization is the practice of comparing the qualitative and quantitative properties of herbs to predetermined or defined criteria and guidelines [52].

The WHO has set a strategy for characterization procedures and techniques based on ash values, moisture content, microbial contamination, and chromatographic and spectroscopic evaluations [53,54] for the characterization of herbal materials.

The recent analytical methodologies are critical for Ayurveda and traditional medicines to gain worldwide acceptability. A full and precise pharmacognostic assessment can provide scientific foundations for the superiority of traditional medicines and Ayurvedic formulations [55]. Organoleptic tests need physicochemical research and a pharmacognostical strategy for authenticity and standardization.

The data obtained from the microscopical evaluation can help to find out the presence of adulterants and confirm pure herbal materials, preventing genuine herbal materials from getting impure [56]. Furthermore, it will be beneficial for confirming criteria for the characterization and detection of unorganized crude drugs such as terpenoids, glycosides, saponins, alkaloids, tannins, and flavonoids [57,58]. The qualitative and quantitative study using a microscope, measurement of shape and size, presence of adulterants and contaminants, moisture content, ash value, chemical constituents, and other parameters revealed for the first time [59]. In this regards formulation development of herbal materials in the pharmacopoeia and other standard monographs can act as an important tool for validation [60,61]. Just because of the complexity of the herbal materials, unique procedures and strategies are used to verify their quality, purity, and integrity. Thermo gravimetric analysis (TGA) and differential thermal analysis (DTA) are the two thermal processes for measuring thermal stability, mass measurement, and enthalpy fluctuation and sensitivity of herbal products [62].

HP-TLC TECHNIQUE FOR THE QUALITY CONTROL OF HERBAL PRODUCTS

As a primary quality control component, to develop pharmacopoeial standards of diverse herbal Ayurveda, Siddha, and other therapeutic herb formulations using HPTLC fingerprinting profiles. HPTLC allows phytochemical components of formulations to be revealed, as well as efficacy, safety, and quality assurance [63,64]. Modern analytical methods such as HPTLC are being employed to estimate herbal products [65]. Pharmacognostic and phytochemical assays, as well as physical qualities, are used as quantitative tests for preliminary examination to identify adulteration and alternatives. The HP-TLC technique is frequently utilized for quantitative measurement of phytoconstituents because to its precision and simplicity [66]. Visual identification is achievable even when the number of samples and references are created in microliter strength, in addition to chromatograms and fingerprints digital pictures [67]. It is possible to apply tests and references on the same HP-TLC plate at the same time, which makes comparative research of herbal medications and formulations easier [68].The most demanding and complex challenge in the innovation arena is the quantitative and qualitative identification of active constituents from herbal materials [69]. Procedures such as separation with preparative biological activity do not match the speed of current discovery since they are sluggish and laborious, whereas modern systems seek simple, precise, and rapid processes.

HP-LC METHODS FOR QUALITY CONTROL OF HERBAL DRUGS

Traditional procedures, which include several isolations, can result in the active compound's activity being reduced or altogether lost [70]. As a result of the analytical technique's flexibility, depicting components using HPLC methods is used for the detection of several materials [71]. Herbs and traditional medical preparations made from plant extracts can be analyzed for pharmaceutical constituents with the help of HPLC technology for quality assurance [72]. The components of customary poly herbal drug compositions are separated [73]. HPLC is a compelling analytical technology that has been gaining relevance in the analytical methods of herbs for qualification, quantification, and authenticity. In autumn, drying procedures, plant source, presence of heavy metal, and microbial content are the key factors that affect the quality of herbs and obstruct quality management [74].

HPLC may be a helpful analytical tool for characterization with both quantitative and qualitative estimation of active chemical constituents and biological components in a mixture of herbal preparations. HPLC technology is one of the most accepted techniques for analysis for the estimation of thermo-sensitive substances contained in herbal preparations. With RP-HPLC, it is also viable and effective to analyze poly-component therapeutic herbal preparations. In the detection of various components in herbal preparations, the HPLC and RP-HPLC techniques offer enormous reproducibility and simplicity of computerization. The peaks of the co-eluted components of a mixture of the multi-components of the herbal materials occur throughout the HPLC procedure of that mixture under study due to the intricacy of the matrix [75].

SUPERCRITICAL FLUID CHROMATOGRAPHY (SFC) TECHNIQUE FOR QUALITY CONTROL OF HERBAL MATERIALS

The rising dangers of synthetic compounds and organic solvents to the atmosphere have necessitated a shift in attention to green chemistry principles, as well as a rise in the number of techniques and processes that follow them. Alternatively, SFC is employed to get the primary component from the products [76].

The mobile phase in SFC is made up of compressed carbon dioxide (CO_2) and a little number of organic solvents such as methanol, with the major and minor parts being carbon dioxide and organic solvent respectively.

When compared to liquid chromatographic procedures, the SFC method is more environmentally friendly since it uses fewer organic solvents and has a lower viscosity of the mobile phase due to the lower pressure drop. Because organic solvents are very volatile in nature, extreme caution must be used to avoid dangerous incidents resulting in fires and explosions [77]. Organic solvents have a high purchasing price and are difficult to dispose of, which adds to their disadvantage [78].

The SFC method may be used to analyze lipids, flavonoids, phenolics, alkaloids, saponins, carbohydrates, and a wide range of other analytes. The study of fat-soluble vitamins is becoming increasingly important. In comparison to HPLC and GC techniques, this is a quick analysis. The most essential aspects of the SFC approach are that it takes significantly less time, utilizes a little number of solvents, and is environmentally benign. The analytical SFC technique features quick volume equilibrium and improved lipophilic compound elution. Because there is no water in the system, the SFC approach for residues from the ionization point has an advantage. SFC is also known for being an unusual method of sample preparation. Because of its selective processes and environmentally safe manner, it also finds use in large-scale enterprises [79]. The working area of the SFC is free from oxygen, light, and high temperature, so there is no chance of degradation of the products and therefore the reliability and superiority of the analytical sample are unaltered prior to analysis [80].

INDUCTIVELY COUPLED PLASMA-MASS SPECTROSCOPY (ICP-MS) FOR QUALITY CONTROL OF HERBAL DRUGS

The chemical makeup of medicinal plants plays an important function in the physiological system of live creatures, and herbal medicine can be an important source of trace elements for humans.

The constituent present in medicinal plants is determined by the plant's ability to accumulate elements and the geochemical character of the soil. These therapeutic plants serve as a bridge between living organisms and trace elements. The quality and safety of therapeutic

herbals derived from nature cannot be guaranteed because of quality dilutions caused by industrialization, fertilizer, pesticides, harmful pollutants, and storage.

The trace elements are accessible in two forms in plants: ionic and non-ionic. The metallic elements that cause toxicity while taken in large quantities are chromium (Cr), iron (Fe), copper (Cu), cobalt (Co), and zinc (Zn), but cadmium (Cd), lead (Pb), and mercury (Hg) are very dangerous even in small amounts [81]. The concentration of the element of the active chemical constituent of herbal drugs adds up to both positive and negative impacts on the herbal materials. The methodologies utilized for analytical and chemometric investigations on herbs include ICP-MS and partial induced X-ray emission. These approaches are useful for determining the relationship between the elemental composition of medicinal plants and their influence on the treatment of specific diseases [82]. Heavy metal testing is a critical concern for the quality and safety of herbal materials. The ICP-MS methods are utilized for the detection of the concentration of trace and ultra-trace elements, which provides advancements such as element specificity, detection of multi-isotope, sensitivity, dynamic range, and the potential of very low detection limits [83].

LC-MS AS AN ANALYTICAL TOOL FOR HERBAL DRUGS

While the HPLC technique is employed unaccompanied, it has significant shortcomings in the raw material extract in the complicated analytical process. This disadvantage may be overcome by adopting the LC-MS approach, which is MS attached to HPLC technique that greatly enhances-detection sensitivity [84]. The capabilities of the LC-MS technique include structure elucidation, molecular mass, and fragmentation in formation, retention time, and multi-component detection. The LC-MS combination approach may be used to identify, quantify, and regulate the quality of raw plant material extracts and marketed products [85].

GC-MS FOR QUALITY CONTROL OF HERBAL MATERIALS

Here, GC is coupled with MS. It is used to separate the distinct materials of chemical compound mixtures. The active constituent of the herbal extract can be analyzed using the GC-MS method. The GC-MS approach can be used to determine the essential oil analysis; it can also be used to determine various components of a molecule as well as drug metabolites. Although LC-MS is more responsive than GC-MS, it can analyze heat-sensitive non-volatile components and cannot examine thermally stable volatile components [86]. In a single study, volatile and non-volatile components are identified (qualitatively), components are separated, and distinct chemicals are quantified [87]. It is feasible to conduct multiple chemical analyses at the same time [88].

PROBLEMS AND CHALLENGES IN MARKETING AND COMMERCIALIZATION OF HERBAL DRUGS SOURCES OF REPORT

In general, the Council for International Organizations of Medical Sciences Working Group V recommends that the quality of a report take precedence over its source. As a result, the worth of a report is judged by how well it is written, documented, received, recorded, followed on, clarified, and evaluated, not by who wrote it [89]. However, because the source of a report can affects the information's quality and value, it is an important factor to consider while studying it. The nature, scope, and even feasibility of any follow-up will be influenced by the source. The most common sources of information about adverse events and drug responses are clinical trials and spontaneous reports (voluntary and unsolicited communications on marketed medicinal products). In terms of both amount and type, the latter frequently outnumber the former during a product's life, especially in severe reports.

Herbal medicine providers should be included in national reporting systems for prescribing and dispensing medicines, as well as traditional, complementary, and alternative medicines. Some countries exclude herbal medicine providers who are not doctors, dentists, pharmacists, or nurses from reporting systems.

REPORTS FROM HEALTHCARE PROFESSIONALS

In the post-marketing safety monitoring scenario, adverse drug reaction reporting systems rely mostly on voluntary reporting by health-care professionals, particularly those who are intimately connected to the patient/care consumer (e.g., the patient's primary health care provider or specialist). Many herbal remedies account for a significant portion of non-prescription drugs, and many of them are hurried into this category after completing post-marketing safety testing as prescription drugs. Community pharmacists and nurses can help ensure the safety of these products by working closely with patients and their doctors [90].

REPORTS FROM CONSUMERS

Consumer participation in the use of herbal treatments and herbal products in health care, as well as their concerns about possible adverse effects, should be commended. Consumer complaints of adverse reactions should be taken carefully as a source of information that can help detect signals for unknown herbal medicine effects. Consumer reports may be the only source of information about non-prescription pharmaceuticals, which are frequently taken without consulting a doctor. When it comes to herbal remedies in the non-prescription medical setting, consumer reporting is critical [91]. Consumer reporting, in some form or another, is critical if enough risk information is to be acquired. At present, only a few national regulatory organizations specifically require the collection of direct consumer reports.

MANUFACTURERS

Manufacturers of herbal medicines may be able to provide information about the side effects associated with their products. As part of its regulatory framework, manufacturers in some countries are obligated to disclose bad incidents. Consumers can make complaints directly with companies or their agents. A customer may call a company for a variety of reasons other than fear of a negative outcome. Among these are legal difficulties and, most typically, requests for further information about the goods. Several industry programs that solicit information on adverse responses are another source of consumer complaints, such incidents are not considered spontaneous reports.

REPORTS FROM OTHER SOURCES

As a side effect of herbal medicines, toxicity to the following substances has been observed.

- In nations with limited resources and no pharmacovigilance center, a poison center could play an important role in pharmacovigilance and safety monitoring of natural medicines.
- Drug information centers can also operate as the first point of contact for clinical information. National pharmacovigilance centers and comparable organizations should be able to communicate effectively.
- Consumer advocacy organizations get complaints about any product on the market and may be able to acquire relevant information on herbal treatments.

HERBAL PRODUCTS TARGETED FOR SAFETY MONITORING

To acquire a complete picture of herbal items, it's helpful to conceive of them in terms of the following categories:

Herbal medicines can be classified into two categories, one for use in the prescription medicines category and one for non-prescription medicines.

REPORTING OF SUSPECTED ADVERSE ACTIONS

Even though these guidelines utilize the phrase "national pharmacovigilance center," it is well known that in some countries, the national pharmacovigilance system is made up of a network of national and regional centers. In accordance with the unique national reporting system, reports should be sent to the appropriate center.

The following individuals should submit reports.

- Any findings should be reported to the national pharmacovigilance center by physicians, pharmacists, and nurses who prescribe herbal drugs.
- In most cases, patients/consumers should tell their doctors or herbal medicine providers. They may also report directly to the national pharmacovigilance center, consumer advocacy groups, or manufacturers.
- Manufacturers should directly notify their country's pharmacovigilance center or regulatory authorities.

THE NEED FOR STANDARDIZATION OF HERBAL/TRADITIONAL MEDICINE

The main purpose of standardizing herbal extracts is to ensure that double-blind clinical trials have as much control as feasible. Herbalist Bob Brucea believes that standardization offers benefits. It is always producing a high-quality product using reliable ingredients. When it comes to the quality of most commercial herbs, standardization assures that they contain something and that the correct plant is being used. Many herbalists consider the benefits of standardized herbal products greater accepted by more people, such as doctors and pharmacists, who are accustomed to uniformity and active ingredient concentrations. If phytopharmaceuticals are to be deemed reasonable medicines, they must be standardized and pharmaceutical grade verified, according to Dr. Rudolf Bauer, one of Germany's leading botanical research experts [92]. Most buyers and even many producers believe that standardization is a relatively new phenomenon brought on by the application of current "state-of-the-art" scientific processes to the manufacturing of herbal goods. They would be surprised to learn that the desire for standardized goods has been an industry rallying cry for at least three centuries [93]. In the historical meaning, some producers still refer to a herbal extract made to a constant standard, such as a specific extraction ratio, master recipe, or standard operating process. Customers and the media have been primarily persuaded by marketers that standardization means the product contains a specific level of "active ingredient."

CHALLENGES IN STANDARDIZATION AND DESIGNATING MARKERS

The American Herbal Products Association has now issued some helpful information [94]. The collection of data and controls required to provide content with a reasonable level of uniformity is referred to as "standardization." To limit the inherent variety in natural product composition, quality assurance processes are used in medicinal plan thus ban dry, extraction, and formulation creation. Standardization provides batch-to-batch consistency, validation of the exact amount of extract per dosage unit, and positive control to highlight possible loss or degradation during manufacturing. While ensuring uniform marker content is an important aspect of standardization, it does not automatically indicate a standardized product. Standardization involves stringent quality assurance of both raw materials and manufacturing processes [94]. Standardization includes all steps that lead to a reproducible product without the use of foreign substances (excipients, isolated active principles, etc.).

Others take this in a negative way, supposing it means the product is a synthetically changed extract in which:

1. At the cost of all other ingredients, one or more compounds have been extracted and/or concentrated. Or
2. To reach the declared marker content, the extract is spiked with pure chemicals. or
3. Fractionation and isolation methods produce a material that is no longer natural, but rather a pharmaceutical medicine.

At the heart of the standards, the argument appears to be a great deal of confusion and doubt about what standardization is for and what the process requires. The chemical composition of botanicals varies greatly depending on the species. Wine and coffee have distinct flavors, aromas, and physical characteristics that vary from year to year and region to region, which makes for an ideal comparison. The ultimate chemical profile of a plant and the presence of a certain marker can be influenced by a variety of factors, including intrinsic ones like genetics and external influences like growing, harvesting, drying, and storage conditions. For example, a common garden breeding study of multiple St. John's wort accessions found significant variation in marker content not just throughout growing seasons, but also between the same accessions grown at different sites and between different accessions farmed at the same site. This inherent variability in the chemical makeup of herbs is a major issue, especially for researchers who need to use items of consistent potency to achieve reproducible results. Quantifying the hundreds of chemical components found in herbal material in a timely and cost-effective manner is unachievable with current technology. The compromise solution to this problem is to select a marker compound or compound and then ensure that each batch contains the same amount of those compounds (s). The concept behind this way of preserving consistency is that the quantity of other components fluctuates in proportion to the marker compound and that if each batch contains the same standardized amount of marker, the content of other constituents will be reasonably consistent as well. The market's focus on marking content and homogeneity has benefited unscrupulous entrepreneurs. Adulterated items are much easier to pass off to companies that only check for marker content. The ambiguity of the term "standardization" invites questionable, if not outright fraudulent, behavior. For example, an extraction ratio of 10:1 means that 10 kilograms of plant material was removed to produce 1 kilogram of native extract or 10% extractives. When one kilogram of the extract is recovered from 100 kg of plant material, the proportion of extractives is very low (one percent), but the extraction ratio is quite high (100:1). Such "high strength" extracts can only be obtained using more selective, less polar solvents that will only extract certain molecules or a subset of the plant contents. As a result, while such products may appear to have "high potency," they may only contain a few chemicals and lack medical value. In addition, the residual plant material or marc can be extracted using more polar solvents to produce an extract with many of the usual components. In this way, one batch of plant material can be used to make two bogus products: A "high strength" extract and a "standardized" extract [95]. Marker compounds are one or more constituents found naturally in botanical materials that are chosen for special attention by a researcher or producer. Marker compound amounts, as well as the marker compound (s), are frequently chosen at random.

Several factors may have an impact on this decision, including:

- The constituent's stability(s)
- Analytical ease on a technical level
- Time and money spent on analysis
- Useful for confirming botanical identification.
- Relevance to therapeutic impact (possible)(s)
- Quality or stability indicator for a product
- Other manufacturers or researchers have used it before.

Markers aren't necessarily made up of "active" ingredients. It's possible that the "actives" are unknown, or that the active compounds are extremely unstable or difficult to study. Markers can be used to help determine the correct species (e.g., echinacoside for *Echinacea angustifolia*) or chemotype (e.g., echinacoside for *E. angustifolia*) identification (parthenolide for Feverfew, *Tanacetum parthenium*). Plant components such as flavonoids and ferulic acid, for example, can be used as indicators of product quality during manufacturing or product stability during storage. In some cases, more than one element or a class of constituents may be used as marker compounds.

This could be due to difficulties with analysis, advances in scientific knowledge/technical capabilities, or the use of various markers for various purposes. The "active ingredient," as defined by the WHO/EC, is the entire plant or herbal blend. Experts from across Europe have agreed on a new set of words that identify and distinguish the many functions of marker chemicals. The terms utilized are active principle(s), active marker(s), analytical marker(s), and negative

marker(s). Active principles are chemically well-defined compounds with well-understood pharmacological action, and they are widely regarded as essential contributions to the therapeutic impact. Only few plants fall into this category, in which the product's potency is regarded to be highly connected with the active principle content, allowing for content modifications. A much larger group includes plants for which active markers have been identified. Active markers are chemically identified pharmacologically relevant factors that contribute to efficacy but have not yet been demonstrated to be solely responsible for clinical efficacy. The bulk of herbs fall under the third category, which comprises plants that have yet to be identified as having active principles or active markers. Analytical markers, such as distinctive compounds or major constituents, can be used to define content ranges in certain situations. Allergies, toxins, and chemicals are examples of negative indicators that interfere with bioavailability. Negative markers can be used to detect potentially harmful botanicals, unappealing botanical varieties, or chemical races, as well as unwanted components. Compounds having confirmed *in vitro* action are typically chosen as indicators based on current scientific knowledge, although other, unknown components maybe more important in determining potency. The amount of marker compound to be employed is usually decided at random, often based on the marker's average content in the raw material or semi-purified extract. As a result, marker selection and application are haphazard and uncontrollable. In terms of the markers utilized and the amount of marker targeted, there are several differences across brands. For example, *Panax ginseng* products are considered to be standardized to contain somewhere between seven and seventy percent ginsenosides. Kava (*Piper methysticum*) products are said to contain 30 to 70% kavalactone. Milk thistle (*Silybum marianum*) products reported "standardized" marker content ranges from 30 to 80% silymarin or silybin.

Some *Echinacea purpurea* products are controlled to contain a set quantity of "total phenolic," while others are standardized to contain a certain proportion of citric acid. From a scientific standpoint, standardization of total phenolic content is absurd for a variety of reasons. Phenolics are a huge and poorly understood chemical class that could account for half of all plant components. For example, chlorogenic acid is a common plant component with no immunostimulant effects. Although the media's concerns may be a byproduct of the wide range of approaches used to analyze marker content, standardization has been prominent in the public eye, particularly in terms of allegations about marker content. In response to the controversy, several stakeholder discussions have focused on the industry-wide adoption of established methodologies and certification of product quality. While the substance of the marker is important, many people neglect the fact that the plant must be dealt with first and foremost. This is useless if the plant is not the right one or the plant material is not pure.

The industry's focus on marking content also makes it easier to commit fraud. Methods, method validation, and implementation issues arise in the context of identity and purity research. In the case of identification testing, there is also a significant discrepancy between the best scientific method and the procedures used by the industry. More research is needed in the domain of purity testing to establish if standard purity tests are accurate in detecting impurities in botanicals, particularly finished items. Three other cross-cutting concerns have emerged. The need for authorized reference sources, national quality standards, and pharmacognosy education and training.

AWARENESS OF GOVT. SCHEMES AND SUPPORT

The herbal medicine market is dominated by small and medium-sized firms, and many of these businesses and entrepreneurs are ignorant of the government's activities and support for the industry. Due to a lack of education and awareness, India lacks quality control and good agriculture and collection techniques. Growers aren't well-informed on GACP and aren't aware of it. Furthermore, because providing education and essential information requires operational costs, competent management, and time, industries and associations are not interested in doing so. Proper branding and distribution of herbal drugs to medical experts and the public through print and electronic media are equally difficult jobs to boost product sales and revenue generation [5].

A survey on the regulation and commercialization of Indian herbal drugs found insufficient standardization and quality control of raw materials and finished products, insufficient regulatory guidelines concerning GMP, non-application of GACP, weak implementation of the DCA-1940, and diverse regulatory requirements in different countries [5]. Most of the raw plant material is historically imported from China, India, and Eastern European countries by companies producing herbal pharmaceuticals all around the world. As the industry evolves, companies have implemented additional quality control measures such as testing facilities for active chemicals, purity, and bacterial contamination. For marketing authorization, the Indian DCA (1940) does not require any safety or efficacy trials, although other countries' laws are more stringent [96]. Most Indian herbal remedies are promoted as dietary supplements in the US because the US DSHEA (1994) does not require the submission of any safety or efficacy proof for marketing permission [5]. A key element affecting the quality of herbal medicinal goods is the lack of adequate regulatory rules for the manufacturing process. Even though GMP compliance is required under Schedule T of the DCA (since 2006), only a few firms in the Indian herbal sector follow GMP (1940) [97,5]. Unlike "prescription medications," which are mainly controlled by physicians, most traditional medical goods in India are sold as over-the-counter drugs, and their market is typically affected by advertisement and client desire [5]. To gain a firm presence in both the domestic and foreign markets, it is also vital to generate evidence-based data on the safety and efficacy of herbal products [12]. India must deal with well-planned plant cultivation, postharvest technologies, and plant processing, as well as high-tech manufacturing, quality control, research and extension, patenting ease, and an effective plant marketing strategy. For efficient worldwide commercialization, governments must harmonize their regulatory frameworks. Traditional herbal therapies that have gained traction in China and the Indian subcontinent require special and quick attention, as they will soon be ruling over the entire planet.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Herbal medicine makes a very tiny contribution to modern healthcare, which now has a market worth billions of dollars. This study looks at the scope and potential of herbal pharmaceuticals, as well as the problems and obstacles that herbal pharma production companies are now facing. The situation has now altered, and herbal treatments are becoming increasingly popular due to their great efficacy, safety, and synergistic effect. Herbal medication formulation stability is a crucial concern because it impacts the quality and efficacy of the drug. Novel tactics for minimizing drug instability, such as the use of suspension, biodegradable cellulose, therapeutic proteins, nanoparticles, and emulsifiers, can be particularly beneficial. When it comes to medication stability, preventing drug deterioration due to environmental factors is also a big problem [20]. Proper requirements, including packaging and container, must be followed to ensure medicine stability. Because side effects and toxicity of herbal treatments have been documented, such as kidney damage, stone formation, acute neuropathy, and newborn mortality, pharmacokinetics and ADME research is crucial to ensuring herbal therapies' efficacy, toxicity, and safety profile. The most important stage of herbal medication development, which includes clinical trials and ethics, validates efficacy, safety, and toxicity levels [20]. To compete with current allopathic treatments and survive in the international drug market, such confirmation is required. Competent authority regulations for herbal medication quality and safety requirements are critical for herbal medicine manufacturers to preserve the quality of their goods [98]. Due to a lack of regulations, herbal producers, industries, and growers are unaware of appropriate agriculture and collection methods (GACP) as well as correct storage practices. It's worth noting that only herbal pharmaceuticals that

follow international rules and GACP criteria have a chance to flourish and establish themselves in the worldwide market. Due to flaws and shortcomings in quality production, standardization, business law, and regulatory requirements, commercialization, and marketing of herbal drugs are the hardest and most arduous tasks in today's drug period [39]. Poor raw material quality, microbiological contamination, and heavy metal deposition hamper the Indian herbal treatment market at every stage of production, from cultivation to manufacturing. Such concerns hamper the herbal industry's growth, and the FDA prohibits slow-quality and tainted drugs from accessing the global market [99]. Herbal drug manufacturing is a continuous process that follows WHO recommendation to implement GACP and GMP to ensure the standard and quality of herbal medicines [100]. To avoid any delays in new drug registration, proper application of drug-controlled authority laws through establishment harmonization is required. Herbal companies, manufacturers, and entrepreneurs should be aware of the government's business and market growth strategy and support high-quality, safe medications, which are updated on a regular basis. Herbal medicine makes a very tiny contribution to modern healthcare, which now has a market worth billions of dollars. This is due to a lack of knowledge, technical, and regulatory challenges, a lack of research motivation, pharmaceutical companies, and the industry's little market engagement.

AUTHORS CONTRIBUTION

The review paper was written with the combined effort and contribution of all the authors. Prof. C. M. Hossain has decided on the title of the review article and designed the structure of the paper. Moreover, he has prepared, reviewed, and edited the original draft of the review article with detailed conceptualization. Dr. Meeta Gera has written the Introduction, State of the art and market value of herbal drugs, along with this, Awareness of Govt. schemes and support with detailed discussion and conclusion part. Dr. Kazi Asraf Ali wrote the Problems and Challenges associated with herbal drugs, such as in clinical trials and ethics and in marketing and commercialization of drugs. Also, he has written the Quality control and safety regulations of herbal medicine.

CONFLICTS OF INTERESTS

The authors declare no potential conflict of interest.

AUTHORS FUNDING

Not Applicable.

REFERENCES

1. Meganck RM, Baric RS. Developing therapeutic approaches for twenty-first-century emerging infectious viral diseases. Nat Med 2021;27:401-10. doi: 10.1038/s41591-021-01282-0, PMID 33723456
2. El-Saadony MT, Zabermawi NM, Zabermawi NM, Burollus MA, Shafi ME, Alagawany M, *et al*. Nutritional aspects and health benefits of bioactive plant compounds against infectious diseases: A review. Food Rev Int 2021:1-23. doi: 10.1080/87559129.2021.1944183
3. Wu C, Lee SL, Taylor C, Li J, Chan YM, Agarwal R, *et al*. Scientific and regulatory approach to botanical drug development: A US FDA perspective. J Nat Prod 2020;83:552-62. doi: 10.1021/acs.jnatprod.9b00949, PMID 31977211
4. Pan SY, Zhou SF, Gao SH, Yu ZL, Zhang SF, Tang MK, *et al*. New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. Evid Based Complement Alternat Med 2013;2013:627375. doi: 10.1155/2013/627375, PMID 23634172
5. Sahoo N, Manchikanti P. Herbal drug regulation and commercialization: An Indian industry perspective. J Altern Complement Med 2013;19:957-63. doi: 10.1089/acm.2012.0275, PMID 23829812
6. Shaheen S, Ramzan S, Khan F, Ahmad M. Adulteration in Herbal Drugs: A Burning Issue. Berlin: Springer International Publishing; 2019. p. 1-179.
7. Bandaranayake WM. Quality Control, Screening, Toxicity, and Regulation of Herbal Drugs. Modern phytomedicine: Turning Medicinal Plants into Drugs. Weinheim: WILEY-VCH Press; 2006. p. 25-57.
8. Parasuraman S, Thing GS, Dhanaraj SA. Polyherbal formulation: Concept of Ayurveda. Pharmacogn Rev 2014;8:73-80. doi: 10.4103/0973-7847.134229, PMID 25125878
9. Mukeshwar P, Mousumi D, Shobit G, Surender KC. Phytomedicine: An ancient approach turning into future potential source of therapeutics. J Pharmacogn Phytother 2011;3:27-37.
10. Gera M, Sharma N, Ghosh M, Huynh DL, Lee SJ, Min T, *et al*. Nanoformulations of curcumin: An emerging paradigm for improved remedial application. Oncotarget 2017;8:66680-98. doi: 10.18632/oncotarget.19164, PMID 29029547
11. Gan BH, Gaynord J, Rowe SM, Deingruber T, Spring DR. The multifaceted nature of antimicrobial peptides: Current synthetic chemistry approaches and future directions. Chem Soc Rev 2021;50:7820-80. doi: 10.1039/d0cs00729c, PMID 34042120
12. Parveen B, Parveen A, Parveen R, Ahmad S, Ahmad M, Iqbal M. Challenges and opportunities for traditional herbal medicine today with special reference to its status in India. Ann Phytomed 2020;9:97-112. doi: 10.21276/ap.2020.9.2.8
13. Sen S, Chakraborty R. Revival, modernization and integration of Indian traditional herbal medicine in clinical practice: Importance, challenges and future. J Trad Complement Med 2017;7:234-44. doi: 10.1016/j.jtcme.2016.05.006, PMID 28417092
14. Newman DJ, Cragg GM, Snader KM. The influence of natural products upon drug discovery. Nat Prod Rep 2000;17:215-34. doi: 10.1039/a902202c, PMID 10888010
15. Bussmann RW, Malca-García G, Glenn A, Sharon D, Chait G, Díaz D, *et al*. Minimum inhibitory concentrations of medicinal plants used in Northern Peru as antibacterial remedies. J Ethnopharmacol 2010;132:101-8. doi: 10.1016/j.jep.2010.07.048, PMID 20678568
16. Gera M, Kim N, Ghosh M, Sharma N, Huynh DL, Chandimali N, *et al*. Synthesis and evaluation of the antiproliferative efficacy of BRM270 phytocomposite nanoparticles against human hepatoma cancer cell lines. Mater Sci Eng C Mater Biol Appl 2019;97:166-76. doi: 10.1016/j.msec.2018.11.055, PMID 30678901
17. Thakkar S, Anklam E, Xu A, Ulberth F, Li J, Li B, et al. Regulatory landscape of dietary supplements and herbal medicines from a global perspective. Regul Toxicol Pharmacol 2020;114:104647. doi: 10.1016/j.yrtph.2020.104647, PMID 32305367
18. Neergheen-Bhujun VS. Underestimating the toxicological challenges associated with the use of herbal medicinal products in developing countries. BioMed Res Int 2013;2013:804086. doi: 10.1155/2013/804086, PMID 24163821
19. Oketch-Rabah HA, Roe AL, Rider CV, Bonkovsky HL, Giancaspro GI, Navarro V, *et al*. United states pharmacopeia (USP) comprehensive review of the hepatotoxicity of green tea extracts. Toxicol Rep 2020;7:386-402. doi: 10.1016/j.toxrep.2020.02.008, PMID 32140423
20. Prabhakar P, Mamoni B. Technical problems, regulatory and market challenges in bringing herbal drug into mainstream of modern medicinal practices. Res J Biotechnol 2021;16:3.
21. Baliga MS, Bhat HP, Joseph N, Fazal F. Phytochemistry and medicinal uses of the bael fruit (*Aegle marmelos* Correa): A concise review. Food Res Int 2011;44:1768-75. doi: 10.1016/j.foodres.2011.02.008
22. Deo YK, Reddy RK. Critical review on pharmacological properties of Brahmi. Int J Ayurveda Med Int J Am Med 2013;4:92-9. doi: 10.47552/ijam.v4i2.238
23. Rezazadeh F, Moshaverinia M, Motamedifar M, Alyaseri M. Assessment of anti HSV-1 activity of *Aloe vera* gel extract: An *in vitro* study. J Dent (Shiraz) 2016;17:49-54. PMID 26966709
24. Balammal G, Sekar BM, Reddy JP. Analysis of herbal medicines by modern chromatographic techniques. Int J Preclin Pharm Res 2012;3:50-63.
25. Pal SK, Shukla Y. Herbal medicine: Current status and the future. Asian Pac J Cancer Prev 2003;4:281-8. PMID 14728584
26. Nema AK, Agarwal A, Kashaw V. Hepatoprotective activity of Leptadenia reticulata stems against carbon tetrachloride-induced hepatotoxicity in rats. Indian J Pharmacol 2011;2:360-74.
27. Prabhu TP, Panneerselvam P, Kumar RV, Atlee WC, Subramanian SB. Anti-inflammatory, anti arthritis and analgesic effect of ethanolic extract of whole plant of *Merremia emarginata* Burm.f. Cent. Eur J Exp Biol 2012;1:94-9.
28. Patel P, Patel D, Patel N. Experimental investigation of anti-rheumatoid activity of *Pleurotus sajor caju* in adjuvant-induced arthritic rats. Chin J Nat Med 2012;10:269-74.
29. Karbwang J, Crawley FP, Na-Bangchang K, Maramba-Lazarte C. Herbal medicine development: Methodologies, challenges, and

issues. Evid Based Complement Alternat Med 2019;2019:4935786. doi: 10.1155/2019/4935786, PMID 31687036
30. Bansal G, Suthar N, Kaur J, Jain A. Stability testing of herbal drugs: Challenges, regulatory compliance and perspectives. Phytother Res 2016;30:1046-58. doi: 10.1002/ptr.5618, PMID 27073177
31. Cassileth BR, Heitzer M, Wesa K. The public health impact of herbs and nutritional supplements. Pharm Biol 2009;47:761-7. doi: 10.1080/13880200902991581, PMID 19890479
32. World Health Organization. Guidelines for the Regulation of Herbal Medicines in the South-East Asia Region. WHO Regional Office for South-East Asia. Geneva: World Health Organization; 2004.
33. World Health Organization. WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems. Geneva: World Health Organization; 2004.
34. World Health Organization. National Policy on Traditional Medicine and Regulation of Herbal Medicines: Report of a WHO Global Survey. Geneva: World Health Organization; 2005.
35. Bansal D, Hota D, Chakrabarti A. Research methodological issues in evaluating herbal interventions. Open Access J Clin Trials 2010;2:15-21.
36. Parveen A, Parveen B, Parveen R, Ahmad S. Challenges and guidelines for clinical trial of herbal drugs. J Pharm Bioallied Sci 2015;7:329-33. doi: 10.4103/0975-7406.168035, PMID 26681895
37. Ameh SJ, Obodozie OO, Babalola PC, Gamaniel KS. Medical herbalism and herbal clinical research: A global perspective. Br J Pharm Res 2011;1:99-123. doi: 10.9734/BJPR/2011/403
38. Wei SY, Chen Y, Xu XY. Progress on the pharmacological research of puerarin: A review. Chin J Nat Med 2014;12:407-14. doi: 10.1016/S1875-5364(14)60064-9, PMID 24969520
39. Ernst E. The efficacy of herbal medicine-an overview. Fundam Clin Pharmacol 2005;19:405-9. doi: 10.1111/j.1472-8206.2005.00335.x, PMID 16011726
40. Kleinman A, Eisenberg L, Good B. Culture, illness, and care: Clinical lessons from anthropologic and cross-cultural research. Ann Intern Med 1978;88:251-8. doi: 10.7326/0003-4819-88-2-251, PMID 626456
41. Lai SL. Ch 1. Guangdong: In: Clinical Trials of Traditional Chinese Materia Medica. New Delhi: People's Publishing House; 2000.
42. Walsh EL, Ashe S, Walsh JJ. Nature's migraine treatment: Isolation and structure elucidation of parthenolide from *Tanacetum parthenium*. J Chem Educ 2012;89:134-7. doi: 10.1021/ed200064h
43. Buchanan DR, White JD, O'Mara AM, Kelaghan JW, Smith WB, Minasian LM. Research-design issues in cancer-symptom-management trials using complementary and alternative medicine: Lessons from the national cancer institute community clinical oncology program experience. J Clin Oncol 2005;23:6682-9. doi: 10.1200/JCO.2005.10.728
44. Tomassoni AJ, Simone K. Herbal medicines for children: An illusion of safety? Curr Opin Pediatr 2001;13:162-9. doi: 10.1097/00008480-200104000-00014, PMID 11317060
45. World Health Organization. Traditional and modern medicine: harmonizing the two approaches: A Report of the Consultation Meeting on Traditional and Modern Medicine: Harmonizing the Two Approaches. Beijing, China: World Health Organization; 1999.
46. US Food and Drug Administration. Dietary Supplement Health and Education Act of 1994. Available from: https://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/ucm148003.html [Last accessed on 2021 Nov].
47. US Food and Drug Administration. Regulatory Framework of DSHEA of 1994. Available from: https://www.fda.gov/NewsEvents/Testimony/ucm115163.htm [Last accessed on 2021 Nov].
48. National Institute of Health (NIH) Office of Dietary Supplements. Kava; 2021. Available from: https://www.ods.od.nih.gov/health_information/kava.aspx [Last accessed on 2021 Nov].
49. Skalli S, Soulaymani Bencheikh RS. Safety monitoring of herb-drug interactions: A component of pharmacovigilance. Drug Saf 2012;35:785-91.
50. Zhou J, Ouedraogo M, Qu F, Duez P. Potential genotoxicity of traditional Chinese medicinal plants and phytochemicals: An overview. Phytother Res 2013;27:1745-55. doi: 10.1002/ptr.4942, PMID 23420770
51. Kapere KN, Mugisha MK, Anne O. Community perceptions on the use of traditional medicine among people experiencing sexual dysfunctions in Greater Mbarara, Western Uganda. J Pharmacogn Phytochem 2022;11:46-59.
52. Kamble MA, Mane MR, Ingole AR, Dhabarde DM. Standardization of some marketed herbal formulations used in diabetes. J Adv Res Pharm Sci Pharmacol Interv 2019;2:22-6.
53. Nazim MD, Aslam DM, Khatoon R, Asif DM, Chaudhary SS. Physico-chemical standardization of Hansraj (*Adiantum capillus-veneris*). J Drug Deliv Ther 2018;8:195-203. doi: 10.22270/jddt.v8i6-s.2229
54. Marchese A, Barbieri R, Coppo E, Orhan IE, Daglia M, Nabavi SF, *et al*. Antimicrobial activity of eugenol and essential oils containing eugenol: A mechanistic viewpoint. Crit Rev Microbiol 2017;43:668-89. doi: 10.1080/1040841X.2017.1295225, PMID 28346030
55. Deogade MS, Prasad KS. Standardization of wild Krushnatulasi (*Ocimum tenuiflorum* Linn) leaf. Int J Ayurveda Med 2019;10:52-61. doi: 10.47552/ijam.v10i1.1172
56. Shaheen N, Imam S, Abidi S, Sultan RA, Azhar I, Mahmood ZA. Comparative pharmacognostic evaluation and standardization of *Capsicum annuum* L.(red chili). Int J Pharm Sci Res 2018;9:2807-17.
57. Liu C, Guo DA, Liu L. Quality transitivity and traceability system of herbal medicine products based on quality markers. Phytomedicine 2018;44:247-57. doi: 10.1016/j.phymed.2018.03.006, PMID 29631807
58. Singh Saroya A, Singh J. Mycotoxins in herbal medicines. In: Psychoactive Medicinal Plants and Fungal Neurotoxins. Singapore: Springer; 2020. p. 119-21.
59. Rashid S, Zafar M, Ahmad M, Lone FA, Shaheen S, Sultana S, *et al*. Microscopic investigations and pharmacognostic techniques used for the standardization of herbal drug *Nigella sativa* L. Microsc Res Tech 2018;81:1443-50. doi: 10.1002/jemt.23110, PMID 30351462
60. Zhang J, Wider B, Shang H, Li X, Ernst E. Quality of herbal medicines: Challenges and solutions. Complement Ther Med 2012;20:100-6. doi: 10.1016/j.ctim.2011.09.004, PMID 22305255
61. Fernandes FH, Salgado HR. Gallic acid: Review of the methods of determination and quantification. Crit Rev Anal Chem 2016;46:257-65. doi: 10.1080/10408347.2015.1095064, PMID 26440222
62. Guimarães GP, Santos RL, Brandão DO, Cartaxo-Furtado NA, Cavalcanti AL, Macedo RO. Thermoanalytical characterization of herbal drugs from *Poincianella pyramidalis* in different particle sizes. J Therm Anal Calorim 2018;131:661-70. doi: 10.1007/s10973-016-6076-4
63. Kannan NB, Devi GV, John A, Lekha JS, Natarajan M, Kanagarajan A. Pharmacognostic evaluation and HPTLC fingerprinting of Pirantai Vatakam, a Siddha formulation. J Phytopharmacol 2019;8:33-7. doi: 10.31254/phyto.2019.8201
64. Do T, Santi I, Reich E. A harmonized HPTLC method for identification of various caffeine containing herbal drugs, extracts, and products, and quantitative estimation of their caffeine content. J Liquid Chromatogr Rel Technol 2019;42:274-81. doi: 10.1080/10826076.2019.1585612
65. Chewchida S, Vongsak B. Simultaneous HPTLC quantification of three caffeoylquinic acids in *Pluchea indica* leaves and their commercial products in Thailand. Rev Brasil Farmacogn 2019;29:177-81. doi: 10.1016/j.bjp.2018.12.007
66. Mangal AK, Tewari D, Shantha TR, Bansal S, Mangal M. Pharmacognostical standardization and HPTLC fingerprinting analysis of *Crocus sativus*. Indian J Trad Knowl 2018;17:592-7.
67. Tomar V, Beuerle T, Sircar D. A validated HPTLC method for the simultaneous quantifications of three phenolic acids and three withanolides from *Withania somnifera* plants and its herbal products. J Chromatogr B Analyt Technol Biomed Life Sci 2019;1124:154-60. doi: 10.1016/j.jchromb.2019.06.009, PMID 31200247
68. Alam P, Kamal YT, Alqasoumi SI, Foudah AI, Alqarni MH, Yusufoglu HS. HPTLC method for simultaneous determination of ascorbic acid and gallic acid biomarker from freeze dry pomegranate juice and herbal formulation. Saudi Pharm J 2019;27:975-80. doi: 10.1016/j.jsps.2019.07.006, PMID 31997904
69. Hamburger M. HPLC-based activity profiling for pharmacologically and toxicologically relevant natural products-principles and recent examples. Pharm Biol 2019;57:328-34. doi: 10.1080/13880209.2019.1606261, PMID 31057026
70. Hemdan A, Tawakol SM. HPLC-UV chromatographic methods for detection and quantification of undeclared withdrawn synthetic medications in counterfeit herbal medicines with confirmation by HPLC-PDA and mass spectrometry. Chromatographia 2018;81:777-83. doi: 10.1007/s10337-018-3502-8
71. Walters NA, de Villiers A, Joubert E, de Beer D. Improved HPLC method for rooibos phenolics targeting changes due to fermentation. J Food Compost Ann 2017;55:20-9. doi: 10.1016/j.jfca.2016.11.003
72. Nag M, Kar A, Chanda J, Mukherjee PK. RP-HPLC analysis of methanol extract of *Viscum* articulatum. J Ayurveda Integr Med 2020;11:277-80. doi: 10.1016/j.jaim.2018.02.135, PMID 30638917
73. Raclariu AC, Paltinean R, Vlase L, Labarre A, Manzanilla V, Ichim MC, *et al*. Comparative authentication of *Hypericum perforatum* herbal products using DNA metabarcoding, TLC and HPLC-MS. Sci Rep 2017;7:1291. doi: 10.1038/s41598-017-01389-w, PMID 28465563

74. Gitea D, Vicas S, Gitea MA, Nemeth S, Tit DM, Pasca B, *et al*. HPLC screening of bioactives compounds and antioxidant capacity of different *Hypericum* species. Rev Chim 2018;69:305-9. doi: 10.37358/RC.18.2.6095
75. Govindarajan R, Tejas V, Pushpangadan P. High-performance liquid chromatography (HPLC) as a tool for standardization of complex herbal drugs. J AOAC Int 2019;102:986-92. doi: 10.5740/jaoacint.18-0378, PMID 30558698
76. Sánchez-Camargo ADP, Parada-Alonso F, Ibáñez E, Cifuentes A. Recent applications of on-line supercritical fluid extraction coupled to advanced analytical techniques for compounds extraction and identification. J Sep Sci 2019;42:243-57. doi: 10.1002/jssc.201800729, PMID 30156751
77. Liu TT, Cheong LZ, Man QQ, Zheng X, Zhang J, Song S. Simultaneous profiling of Vitamin D metabolites in serum by supercritical fluid chromatography-tandem mass spectrometry (SFC-MS/MS). J Chromatogr B Analyt Technol Biomed Life Sci 2019;1120:16-23. doi: 10.1016/j.jchromb.2019.04.050, PMID 31060022.
78. Zhong J, Wang X, editors. Evaluation Technologies for Food Quality. United Kingdom: Woodhead Publishing; 2019.
79. Murcia-Morales M, Cutillas V, Fernández-Alba AR. Supercritical fluid chromatography and gas chromatography coupled to tandem mass spectrometry for the analysis of pyrethroids in vegetable matrices: A comparative study. J Agric Food Chem 2019;67:12626-32. doi: 10.1021/acs.jafc.9b00732, PMID 31062971
80. Huang Y, Wang T, Fillet M, Crommen J, Jiang Z. Simultaneous determination of amino acids in different teas using supercritical fluid chromatography coupled with single quadrupole mass spectrometry. J Pharm Anal 2019;9:254-8. doi: 10.1016/j.jpha.2019.05.001, PMID 31452963
81. Oral EV, Tokul-Ölmez Ö, Yener İ, Firat M, Tunay Z, Terzioğlu P, *et al*. Trace elemental analysis of allium species by inductively coupled plasma-mass spectrometry (ICP-MS) with multivariate chemometrics. Anal Lett 2019;52:320-36. doi: 10.1080/00032719.2018.1460376
82. Rao JC, Gowri Naidu B, Sarita P, Srikanth S, Raju GJ. Elemental analysis of *Pterocarpus santalinus* by PIXE and ICP-MS: Chemometric approach. J Radioanal Nucl Chem 2019;322:129-37. doi: 10.1007/s10967-019-06598-3
83. Tokalıoğlu Ş, Dokan FK, Köprü S. ICP-MS multi-element analysis for determining the origin by multivariate analysis of red pepper flakes from three different regions of Turkey. LWT 2019;103:301-7. doi: 10.1016/j.lwt.2019.01.015
84. Marchetti L, Pellati F, Graziosi R, Brighenti V, Pinetti D, Bertelli D. Identification and determination of bioactive phenylpropanoid glycosides of *Aloysia polystachya* (Griseb. et Moldenke) by HPLC-MS. J Pharm Biomed Anal 2019;166:364-70. doi: 10.1016/j.jpba.2019.01.033, PMID 30708235
85. Wu W, Jiao C, Li H, Ma Y, Jiao L, Liu S. LC-MS based metabolic and metabonomic studies of *Panax ginseng*. Phytochem Anal 2018;29:331-40. doi: 10.1002/pca.2752, PMID 29460310
86. Zhang A, Sun H, Wang X. Mass spectrometry-driven drug discovery for development of herbal medicine. Mass Spectrom Rev 2018;37:307-20. doi: 10.1002/mas.21529, PMID 28009933
87. Zhang HQ, Liu P, Duan JA, Dong L, Shang EX, Qian DW, *et al*. Comparative analysis of carbohydrates, nucleosides and amino acids in different parts of *Trichosanthes kirilowii* Maxim. by (Ultra) high-performance liquid chromatography coupled with tandem mass spectrometry and evaporative light scattering detector methods. Molecules 2019;24:1440. doi: 10.3390/molecules24071440, PMID 30979080
88. Gomathi D, Kalaiselvi M, Ravikumar G, Devaki K, Uma C. GC-MS analysis of bioactive compounds from the whole plant ethanolic extract of *Evolvulus alsinoides* (L.) L. J Food Sci Technol 2015;52:1212-7. doi: 10.1007/s13197-013-1105-9, PMID 25694742
89. Bent S. Herbal medicine in the United States: Review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. J Gen Intern Med 2008;23:854-9. doi: 10.1007/s11606-008-0632-y, PMID 18415652
90. Ernst E. Herb-drug interactions: Potentially important but woefully under-researched. Eur J Clin Pharmacol 2000;56:523-4. doi: 10.1007/s002280000194, PMID 11151739
91. Knöss W, Chinou I. Regulation of medicinal plants for public health-European community monographs on herbal substances. Planta Med 2012;78:1311-6. doi: 10.1055/s-0031-1298578, PMID 22618374
92. Bone K. Standardized Extracts: Neither Poison nor Panacea. Herbal Gram; 2001;53:50-5.
93. Cowen DL. Pharmacopoeias and Related Literature in Britain and America. United Kingdom: Routledge; 2001. p. 1618-847.
94. Pal RS, Mishra A. Quality control assessment of Dhatryadi Ghrita with HPTLC method. Curr Biotechnol 2020;8:104-8. doi: 10.2174/2211550108666190902123809
95. Sen S, Chakraborty R, De B. Challenges and opportunities in the advancement of herbal medicine: India's position and role in a global context. J Herb Med 2011;1:67-75. doi: 10.1016/j.hermed.2011.11.001
96. Verma N. Herbal medicines: Regulation and practice in Europe, United States and India. Int J Herb Med 2013;1:1-5.
97. Ekor M. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front Neurol 2013;4:177.
98. Lee JY, Jun SA, Hong SS, Ahn YC, Lee DS, Son CG. Systematic review of adverse effects from herbal drugs reported in randomized controlled trials. Phytother Res 2016;30:1412-9. doi: 10.1002/ptr.5647, PMID 27196988
99. Ndhlala AR, Stafford GI, Finnie JF, Van Staden J. Commercial herbal preparations in KwaZulu-Natal, South Africa: The urban face of traditional medicine. S Afr J Bot 2011;77:830-43. doi: 10.1016/j.sajb.2011.09.002
100. Hargreaves J, Park JO, Ghisalberti EL, Sivasithamparam K, Skelton BW, White AH. New chlorinated diphenyl ethers from an *Aspergillus* species. J Nat Prod 2002;65:7-10. doi: 10.1021/np0102758, PMID 11809055