



(REVIEW ARTICLE)



## Phytopharmaceutical regulated new class: An Industrial initiative of Ayurvedic drugs towards the advancement of India system of medicine

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World Journal of Advanced Research and Reviews, 2022, 15(03), 407–419

Publication history: Received on 16 August 2022; revised on 21 September 2022; accepted on 23 September 2022

Article DOI: <https://doi.org/10.30574/wjarr.2022.15.3.0949>

### Abstract

**Ethnopharmacological relevance:** The growing demand for medicinal plants and their products has led to safety and efficacy concerns. The evaluation of herbal medicines, registration and regulation are important challenges to their safety and efficacy. The provisions for synthetic drugs do not apply to ayurvedic-based herbal products. Furthermore, the regulatory mechanism for ensuring the quality of herbal medicines has become a top priority for Indian drug regulators and drug manufacturers.

**Aim of study:** The aim of this study is to identify and characterise the different features of Ayurveda-related government policies and efforts. AYUSH and CDSCO design and establish regulations for the development of phytopharmaceutical drugs as necessary, utilizing botanical-based medications that have a long history but have thus far lacked adequate documentation.

**Methods:** We conducted a review of the literature on Ayurveda's history, principles, and current status. We have presented the data in a systematic manner that includes all of the initiatives brought forth by the Indian government. To conduct a thorough and comprehensive analysis, we went through various reports, policies, and ancient Ayurvedic texts, and consulted AYUSH-related websites, such as those run by the Ministry of AYUSH.

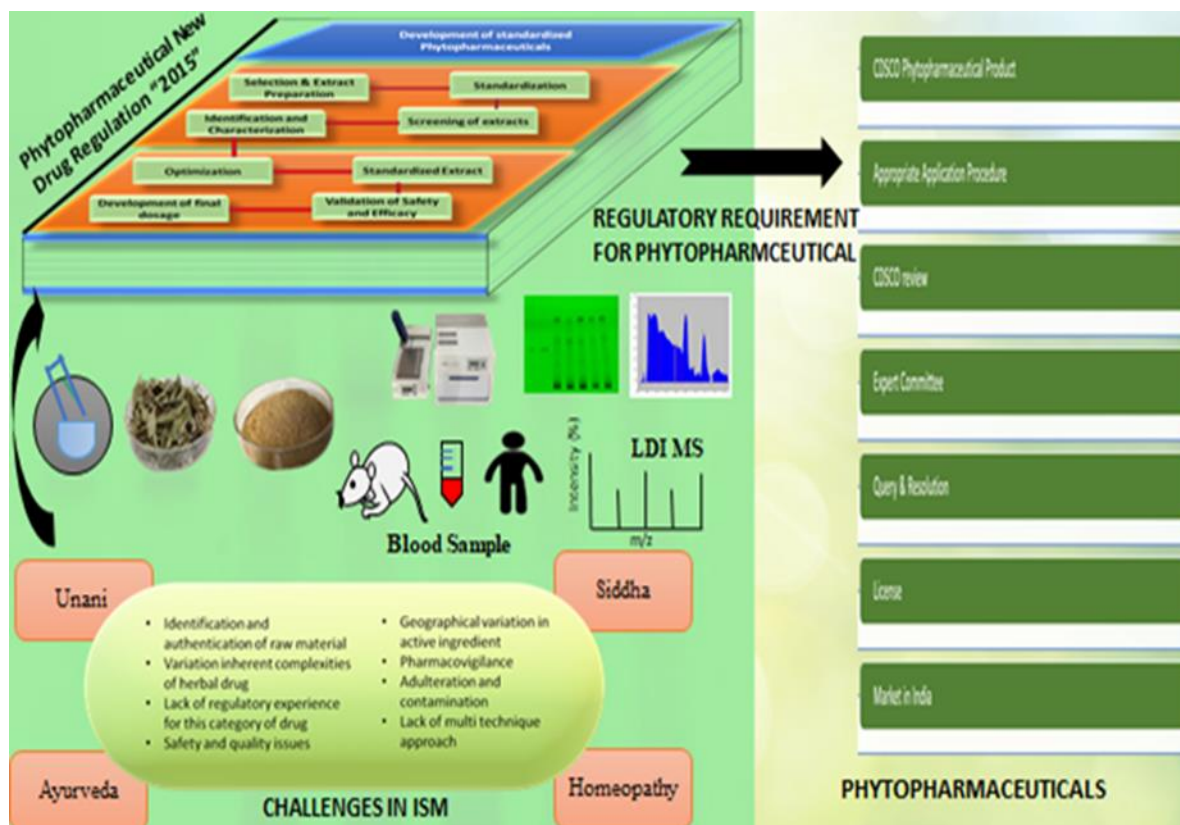
**Results:** The Ministry's objective is to elevate AYUSH systems to the forefront of living and practise, and to make AYUSH methods the preferred method for achieving a healthy nation. The newer class of drugs allows the development of drugs through advanced solvent extraction, fractionation, modern formulation and pharmacokinetics, etc.

**Conclusion:** The promotion and development of Ayurveda is being actively pursued by the government through its policies. The present commentary is designed to highlight core and assembled information on the regulatory requirement in contrast to the new category phytopharmaceuticals under AYUSH. Phytopharmaceuticals may be a balanced approach with guidelines in the United States of America, China, and other countries connecting scientific validation and data generation, including revalidation of AYUSH-regulated product specifications.

**Keywords:** Phytopharmaceuticals; Indian System of medicine; Herbal drugs; Standardization; Quality control.

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## Graphical abstract



## 1. Introduction

Medicinal use of traditional herbs has gained more and more popular support in the modern era, and the opportunity to promote Indian traditional medicine has also grown globally (Ekor 2014). Herbal products are more popular now because they are essential to the healthcare system, and that increased global demand has led to the commercialization of herbal products. Now a days, people from various developed and developing countries are concerned regarding traditional Indian herbal medicines (Kunle et al. 2012). The main impediment to the promotion of traditional Indian herbal products is a lack of drug standardization (Isola 2013). The safety issues with herbal medicinal products arise as a result of a largely unregulated growing market with a lack of effective quality control (Fong 2002). The lack of strict guidelines affects the majority of aspects established in different regulatory systems, such as identifying and assessing safety and efficacy, quality control, and safety monitoring; also discovering and documenting information on traditional medicine/complementary and alternative medicine (Organization 2019).

The vast majority of India's herbal drug manufacturing facilities are GMP-compliant, with most of them being small and medium-sized businesses (Sahoo et al. 2010). However, while representing 70% of India's total exports, approximately 30% of Indian exports are raw materials and finished products, such as herbal extracts (Pan et al. 2014). Traditional herbal treatments are not given the credit they deserve in India since they are promoted as supplements rather than medicines (Sahoo et al. 2010). Additionally, other countries have their own standards that are distinct from India's. Plant-specific characteristics and quality standards, such as permitted limits for heavy metals, pesticides, and microbiological contamination, vary across various nations, according to a global comparison of pharmacopeial standards (Verma 2016). Rules and regulations specific to a country have evolved, but only a subset of them have been put into practice (Sahoo and Manchikanti 2013). Compliance with so many standards has become a major source of concern for Indian manufacturers and traders (Sahoo and Manchikanti 2013). Previously, several regulatory and promotional approaches were taken to combat such issues, but due to the complex nature of herbal medicines, conventional quality control methods are frequently insufficient (Dixon 2001). To address these issues, natural products analysts choose one or more compounds as markers for identification and quality assessment. Several markers, such as taxonomic, chemical, genomic, and proteomic markers, aid in the identification of herbal drug components (Jiang et al. 2010).

Herbal drug components are sometimes identified and authenticated by using marker-based standards (Mukherjee 2019). Because plant extracts are used, multi-marker analysis and storage conditions are important to address. In contrast, the Central Drugs Standards Control Organization (CDSCO) is in charge of phytopharmaceutical regulatory requirements in 2015 (Bhatt 2016). This paper suggests that, in order to be registered as a phytopharmaceutical, a chemical composition is required in addition to regulations defining quality, safety, and efficacy criteria to assess and enable the marketing of herbal medications with chemical components like synthetics. This comment offers insight into the required information and process in making a phytopharmaceutical drug available within the country (Calixto 2000). Phytopharmaceutical drug NDA regulation: Standards including identifying, authenticating, and source of the plant used for extraction and fractionation, extraction and fractionation process, plant pharmaceutical drug formulation details, formulation manufacturing process, stability data, pharmacological information, human studies, and confirmatory clinical trials are all applicable regulatory requirements (Nooreen et al. 2018).

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## 2. Current Status of Indian System of Medicine

An estimated Rs 80 billion (US\$125 million) is generated by the herbal industry in India, which uses approximately 960 plant species for the preparation of botanicals (Sen and Chakraborty 2016). Approximately 3% of total Indian pharmaceutical exports is derived from AYUSH (Ayurveda, Unani, Siddha, and Homeopathy) products (P et al. 2009). However, the world's herbal export market represents only 1% of total global trade. While, ancient traditional medicines in India can be traced to the existence of the AYUSH industry. It has yet to capitalize on emerging market opportunities (Patwardhan et al. 2005). This study assesses the challenges that the Indian herbal drug industry faces in terms of production, commercialization, and wellregulation of traditional or herbal drugs. AYUSH states that the use of over 600 medicinal plant products, 52 minerals, and 50 animal products is commonly seen in Ayurvedic preparations. The cultivation, collection, and processing of herbal medicinal plants are all fraught with difficulties, including contamination during the growing, harvesting, and processing processes (Khare 2004). The three major problems reported for Indian herbal medicines are substitution, adulteration, and heavy metal contamination (Chan 2003). Standardization of raw materials emerges as a significant issue for the Indian herbal industry as the standard of herbal products is called into question (Choudhary and Sekhon 2011). According to the findings of the study, inadequate regulatory guidelines for various aspects of production are a major cause of quality issues with herbal medicinal products (Ekor 2014). Respondents have recommended a detailed regulatory guideline for raw material standardisation and quality control during production (Sahoo and Manchikanti 2013). Additionally, a substantial majority of respondents recommend the development of a single, uniform technical dossier format for submission to the Food and Drug Administration (FDA) for a faster and simpler review process. The harmonisation of pharmacopoeias and the recognition of Indian monographs in other countries would be beneficial for the registration of drugs in multiple countries at the same time. More than half of the manufacturers use the traditional, physical, chemical and physiochemical methods to standardize raw materials and formulations. These tests have a certain amount of limitations due to the fact that there are no standard reference compounds for the herbal or plant compounds used in medicinal preparations (Prakash et al. 2017).

To overcome the inherent difficulties in collecting raw materials, implementation of high-quality agricultural practises (also referred to as GAPs) prior to medicinal plant cultivation and manufacturing methods that use good manufacturing practises (also referred to as GMPs) during the manufacturing process and for the packaging of finished herbal products is critical (Chan 2005). The following is a list of available guidelines for ASU drugs, as mentioned in Table 1. Based on the earliest texts, experts, and clinical experiences, Indian traditional medicine has been supported (Mukherjee 2015). Herbal products are natural and have no side effects. It aids in the acceptance of the traditional medicinal system by the general public. Acceptability of traditional Indian system drugs for providing therapeutic solutions to health problems has grown with the increased cost-effectiveness and comparative safety of traditional Indian system drugs such as Ayurveda, Siddha, and Unani (ASU). Additionally, the demand for proven clinical safety and efficacy of ASU medicines is on the rise (Sen and Chakraborty 2016). Under the supervision of the Ministry of AYUSH, Various Ayurvedic formulations are evaluated in terms of their ability to meet various quality standards and safety benchmarks developed by the Central Council for Research in Ayurvedic Sciences (CCRAS). Even so, only a small number of drugs have been tested for toxicity: A small number of drugs have been tested for toxicity, with 54 being single drugs, 31 being ayurvedic formulations, and 75 being coded drugs (Bhattacharya 2019). To generate scientific evidence on the safety of the most commonly used classical Ayurvedic herbomineral formulations, biological screening of nearly 389 drugs was completed in 2018 (Singh et al. 2020).

**Table 1** Quality, Safety and Toxicity related guidelines for ASU drugs

S. No	Guidelines	Year
1	Quality control method for medicinal plant material	1998
2	Quality control methods for herbal material	2011
3	Laboratory manual for analysis of ayurveda and siddha formulations	2010
4	Quality control for ASU medicine	2008
5	Protocol for testing of ASU medicines	2007
6	General guideline for drug development	2016
7	ASU pharmacopoeias	1989
8	General methodologies & Research evaluation Traditional medicines	2000
9	OECD guidelines	2001
10	Drug and cosmetic act- Schedule Y	1945
11	GCP guideline for ASU medicines	2013
12	Guideline for safety and toxicity evaluation of ayurvedic formulation	2018
13	Guideline for clinical evaluation of ayurvedic Intervention	2016
14	Regulatory requirement for phytopharmaceutical under the purview of CDSCO	2015

According to the new phytopharmaceuticals guidelines, drug development can be expanded through the use of sophisticated techniques such as solvent extraction, fractionation, modern formulation development, and so on (Gupta et al. 2014). Following approval of the New Drug Application by the Central Drugs Standard Control Organization, the new phytopharmaceutical drug would have the same marketing status as a new chemical entity-based drug (Bhosale and Banerjee 2020). The new phytopharmaceutical law is in line with Western-style standards that require scientific review and data collection. This new regulation is expected to aid in the acceptance of herbal products by modern medicine as well as promote scientific innovation and advancement of new drugs derived from herbs and crude drugs (Sen and Chakraborty 2015). Herbal medicines have been used for a long time in systems (Ayurveda, Unani, and Siddha), so efficacy tests are not required for local use. Modified herbal medicines are variations on indigenous herbal medicine or herbal medicine in terms of system shape or dosage form, mode of administration, herbal medicinal ingredients, methods of preparation, and medical indications (Pan et al. 2014).

### 3. Ayurvedic Formulations and Quality Guidelines

Those ayurvedic drugs that were developed and manufactured in accordance with authoritative books listed in the Drug and Cosmetic Act of 1940 included their source of origin in their labelling. The Ayurvedic Formulary of India categorises different types of formulations into distinct dosage forms. Table 2, illustrates varieties of different ayurvedic formulations like Avleh, Bhasma, Churna, Ghrita, Gutika, Guggulu, Kupipakva, Louha, Modaka, Pisti and Taila etc. In this way, 645 monographs of quality standards of Single drugs and 252 monographs of quality standards of multi-ingredient formulation have been published in two parts of the Ayurvedic Pharmacopoeia in thirteen volumes. Hence, 25 quality standards of Single drugs and 252 monographs of quality standards of multi-ingredient formulation are published in the Ayurvedic Pharmacopoeia in thirteen volumes (Pushpendra et al. 2015). In developing Ayurvedic drug pharmacopoeial standards, various identity, purity, and strength assessment parameters are taken into consideration, such as confirmed identification, chemical constituent and permissible limits of heavy metals, pesticide residue and aflatoxins, and microbial load. An equivalent drug list with over 250 medicines is published for the contribution of high-quality Ayurvedic medicines to health facilities across the country, and states are encouraged to obtain such medicines for free distribution to patients via dispensaries and other medical facilities.

**Table 2** Formulation available in the AFI

S. No	Ayurvedic Name	Method of Preparation
1	Asava	The drug is coarsely powdered and Kasaya is prepared and Kasaya is strained and kept in a fermentation vessel add and boiled Sugar, jiggery, or honey and dissolved it. The mouth of the vessel is covered with an earthen lid and the edges sealed with clay-smeared cloth wound in seven consecutive layers.  A constant temperature is maintained for fermentation by keeping the container either in a special room, in an underground cellar, or a heap of paddy. After a specified period, the lid is removed and the contents examined to ascertain whether fermentation has been completed. The fluid is first decanted and then strained after two or three days. When the fine suspended particles settle down, it is strained and bottled.
2	Aristas	The Jaggery or sugar is dissolved in the required quantity of water, boiled, and cooled. This is poured into the fermentation vessel. Fine powder of the drugs is added to the container which is covered with a lid and the edges are sealed with clay smeared cloth wound in seven consecutive layers.
3	Arka	Drugs are soaked in the required quantity of water and boiled. After this vapors get condensed and collected in a receiver. For ensuring the uniformity of Arka, the aliquots were collected in between the active ingredients and then mix.
4	Avaleha or leha and paka	Dissolve the gur in the decoction or liquid and stained to remove the foreign particles. Further, boil the solution on a moderate fire. When the paka is tantuvat remove it from the fire. Churna of herbs are added and mix it vigorously until form a homogenous mixture and mix with ghee or taila during the hot preparation and mix well. When the preparation cool adds the Madhu and mixes it well.
5	Churna	Churna is a fine powder form of drugs. All these herbs and other active ingredients are cleaned dried and powdered together by mechanical means to the fineness of at least 80 mesh.
6	Guggulu	Ayurvedic medicines prepared by the exudates, and obtained from the plant commiphara mukul, are known as Goggulu. There are five different varieties of Goggulu in Ayurvedic Shastra but usually two varieties, mahiskasa and kanaka are preferred for medicinal preparation.
7	Ghritas	Ghrita are preparations in which ghee is boiled with prescribed Kasayas (Decoction) and kalkas of drugs according to formulation as per Ayurvedic formulary.
8	Taila	Tailas are prepared by boiling prescribed kasyas (decoction ) and kalkas of drugs in oils according to the formula prescribed in Ayurvedic formulary.
9	Lepa	The drugs are first made into a fine powder and then mixed with some liquid media like water/ cow's urine/ oil/ ghee/swarasa/decoction etc. to obtain the paste form. This paste is applied over the skin
10	Vati and Gutika	Medicines prepared in the form of tablets or pills are known as vati or gutika, these are made of one or more drugs of plant, animal or mineral origin.
11	Bhasma and Pishti	<i>Bhasma</i> involves the three processes of <i>shodhana</i> , <i>dravana</i> , and <i>marana</i> . The leaves of gold are heated over fire and dipped in sesa ( <i>Sesamum indicum</i> ) oil when its red hot, process is continued seven times separately.
12	Rasa Yoga	Ayurvedic medicines containing mineral drugs as main ingredients are called Rasa rasayan or Rasa-yoga.

The development and revision of Ayurvedic drug standards are carried out in collaboration with the management of the Pharmacopoeia Commission of the Indian System of Medicine. Ayurvedic drug standards are developed and revised in accordance with international standards. Many scientific laboratories, including the Pharmacopoeial Laboratory for Indian Medicine (PLIM), which is designated as an appellate laboratory under the provisions of the Drug and Cosmetic Rules, 1945, are involved in the work of standardisation and SOPs for Ayurvedic drugs, and they make use of a variety of sophisticated equipment and analytical tools to accomplish this task. The existing pharmacopoeia system has achieved significant results; however, an integrated pharmacopoeia infrastructure is being developed to improve coordination and outcomes. To this goal, research undertaken by government-accredited laboratories or organisations are proposed to aid in the creation of the pharmacopoeial standard. This project will determine whether the current pharmacopoeial standard for single and multi-ingredient plant, mineral, metal, and animal-derived products is still sound. Phytochemical standard material used by ASU&H for testing Ayurvedic drugs is appended to quality control standards, including DNA barcoding and fingerprinting of medicinal material. In accordance with the terms of the Drug and Cosmetic Act of 1940 and the rules that accompany it, the drug control cell under the ministry of AYUSH is responsible for the regulatory and quality control of Ayurvedic pharmaceuticals. In addition, a drug control cell is coordinated among state licencing authorities, the Drug Controller, and the Drug Testing Laboratory to enforce legislative restrictions governing the quality control of Ayurvedic and other traditional medicines. Amending regulations is done on a continuous basis, but in accordance with current and future trends in quality control standards for natural medicinal products. Manufacturing companies should be given a high level of trust in order to increase GMP compliance, as well as prescribing shelf life and evidence of drug safety and effectiveness. Furthermore, the government has sanctioned the creation of an additional senior level regulatory position, and steps have been taken to establish a vertical structure for AYUSH drugs within the Central Drug Standard Control Organization, which is governed by the Drugs Control General. The state receives funding to improve its infrastructural and functional capacities for producing, testing, and enforcing the quality of Ayurvedic and other traditional medicines.

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#### 4. Definitions

The term "phytopharmaceutical drug" refers to a purified and standard fraction containing at least four bioactive or phytochemical compounds (qualitatively and quantitatively assessed) from an extract of a medicinal plant or its part for internal or external use by humans or animals for the diagnosis, treatment, mitigation, or prevention of any disease or disorder, but does not include administration by parenteral route as specified in Rule 2 of the Drugs & Cosmetics (D&C) Rules, 1945 (Nooreen et al. 2018).

A Novel Phytopharmaceutical drug that has not been used to any significant extent in the country under the conditions prescribed, recommended, or suggested in the labelling and has not been recognised as effective and safe by the licencing authority mentioned in Rule 21 of the D&C Rules for the proposed claims is considered a new drug, according to Rule 122E of the D&C Rules (Nooreen et al. 2018).

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#### 5. Regulatory Status of Ayurveda Siddha & Unani

The Indian government oversees the Ayurvedic, Unani, and Siddha medical systems, and these systems are also referred to as alternative medical systems, by means of the Drug and Cosmetic Act (D and C) 1940 and the Rules 1945. The regulatory authority is the Department of AYUSH, and it has issued an order stating that no manufacturing or marketing of herbal drugs may take place unless a manufacturing licence is acquired, if applicable. There are two types of ASU medicine, as provided for in the text of Ayurveda, Siddha, and Unani, and patent and/or proprietary medicines, in compliance with the provisions of law. (Katoch et al. 2016). Clinical evidence is not required in order to name and manufacture classical medicines in accordance with formulations outlined in authoritative texts. For example, herbal medicines contain elements mentioned in ayurvedic wordings, but the intellectual intervention or innovation of the inventor makes a distinction between the ingredients and the classic medicine that requires further validation. Validation of safety and efficacy using scientific and evidence-based methodologies not only addresses statutory requirements but also aids in achieving universal adequacy. It also boosts practitioners' confidence and end-user satisfaction with the products. Patent or proprietary ASU medicine is required to meet Good Clinical Practice guidelines since 2010, so that requirement has necessitated the development of current Good Clinical Practice guidelines. The outlined procedures outline the roles and responsibilities of clinical trial sponsors, clinical research investigators, monitors, and the like. In addition, this study had to comply with strict scientific and methodological standards and requirements to ensure ASU intervention-based clinical studies were done in accordance with those standards and methods (Samal 2017). It also concludes that clinical trial results and findings are accurately recorded, analysed, and reported. As a result, it is assumed that clinical research produces high-quality data that is acceptable to regulatory authorities for product registration or marketing approval, particularly for nonclassical or non-generic formulations

(Burrows). Also, to ensure the quality of herbal medicines, medicines were required to include the date of expiration on the label of the container or package. ASU medicines must be accompanied by proof of shelf life or expiration date which is substantiated with real-time stability studies as approved in the Ayurvedic Pharmacopoeia of India (Anzar et al. 2019). The new phytopharmaceutical regulation gives manufacturers the freedom to use more advanced extraction processes, potentiating techniques, as well as newer formulations and process development techniques. Better understanding of phytopharmaceutical pharmacokinetics and bioavailability will help develop rational dosage regimens. Pharmacokinetic data suggests that formulation considerations can lead to effective and safe products. New Phytopharmaceutical regulation is consistent with regulations from around the world that regulate the generation of scientific evaluation and data generation. This new regulation is expected to market innovations and the development of new drugs from botanicals in a highly scientific manner, as well as to aid in the acceptance of herbal products by the modern medical community. It may stimulate academic, research, and industry interest in (Khare 2004) phytopharmaceutical drug development. All botanicals' investigational new drug application filing process in the USFDA and other European countries could be strengthened by all of these factors (Patwardhan et al. 2005).

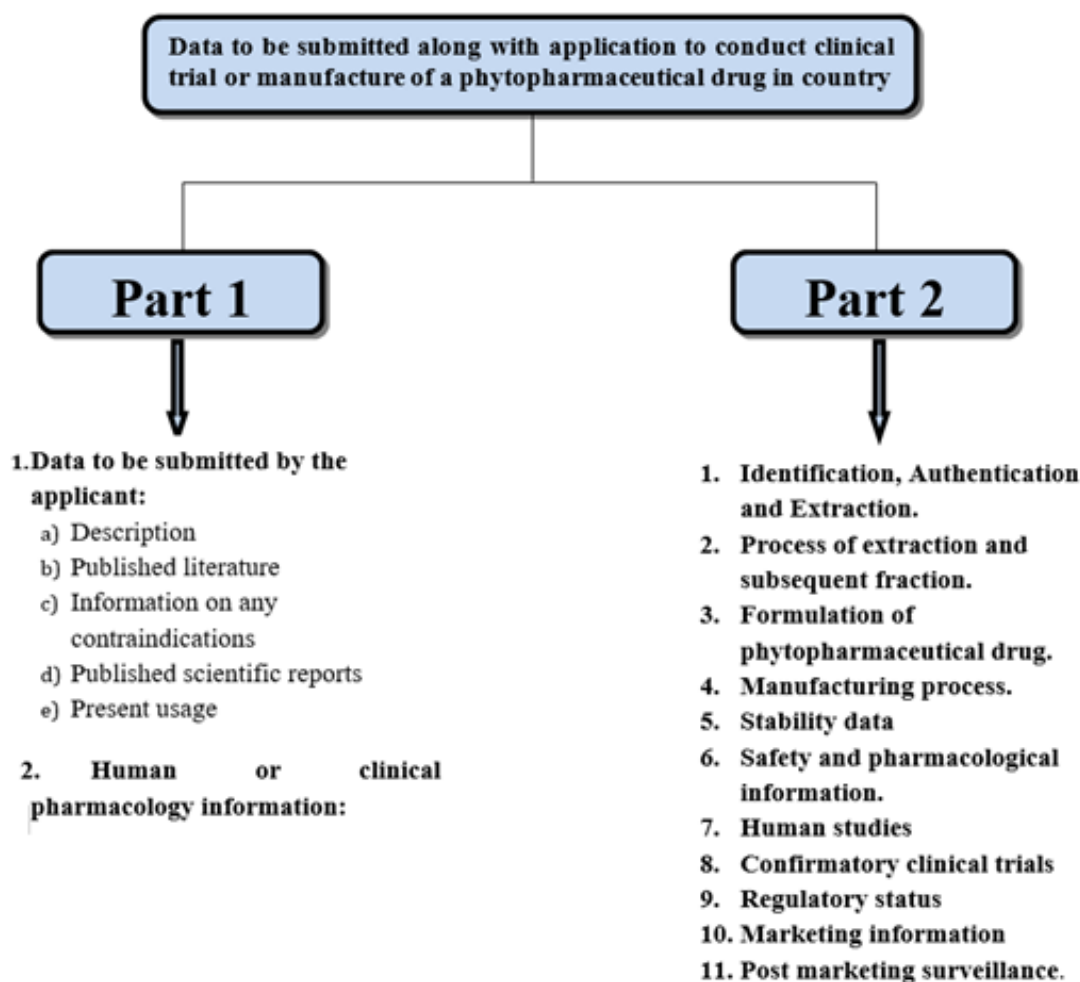
**Table 3** How Ayurvedic, Siddha and Unani differ from phytopharmaceutical drug

S.No	ASU Under section 3 of D & C Act 1940	Phytopharmaceutical drug
1	Classical ASU drugs as mentioned in the authoritative books of ASU system drugs, which are manufactured and named in accordance with the formulations described in the authoritative texts.	Fraction of crude extract.
2	Issue of license to manufacture is based on citation in authoritative books and published literature, unless the drug is meant for a new indication when proof of effectiveness is required.	Purified and standardized fraction with defined minimum four bio-active or phytochemical compounds (qualitatively and quantitatively assessed).
3	Issue of a license to manufacture requires proof of effectiveness, based on the pilot study as per relevant protocol for ASU drugs.	Promote the integration of Indian system of medicine along with the mainstream treatment method with chemical pharmaceuticals.  Promote innovations and development of new drugs from botanicals in a scientific way and would help in the acceptance of the use of herbal products by modern medical profession
5	Ayurveda Siddha and Unani medicine are concerned; it is under the purview of Department of AYUSH.	Phytopharmaceuticals on the other hand are regulated by the Central Drugs Standards Control Organization (CDSCO).
6	Ayurvedic, Siddha or Unani drugs include all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of (disease or disorder in human beings or animals, and manufactured) exclusively in accordance with the formulae described in, the authoritative books of Ayurvedic, Siddha and Unani systems of medicine specified in the first Schedule.	Phytopharmaceutical drugs are fraction of crude extract and are distinctly differentiated by being purified and standardized.



### 5.1. Ayurvedic, Siddha, or Unani (ASU) under Section 3 (a) & (h) of Drugs & Cosmetic Act 1940 differ from Phytopharmaceutical drug

Medicinal products classified as Ayurvedic, Siddha, or Unani (ASU) are distinguished by their purity and standardisation, while other kinds of drugs are also Ayurvedic, Siddha, or Unani (ASU) medications for internal or external use, or for disease or disorder in humans or animals, and are produced solely by the formulae mentioned in the authoritative books of Ayurvedic, Siddha, and Unani systems of medicine identified in Schedule 1, mentioned in Table 3. With the latest research on herbal genomics, a well-designed chemical and biological analysis platform is now available for polyherbal products with multiple active components. It is used to understand the standard of traditional marker-based analysis medications (Bhattacharya et al. 2002). The phytopharmaceutical will promote the integration of the Indian medical system with the conventional treatment method using chemical pharmaceuticals. This new drug class regulation in India is divided into two parts: part I contains data to be submitted by the applicant and part II contains data generated by the applicant as illustrated in Figure 1.

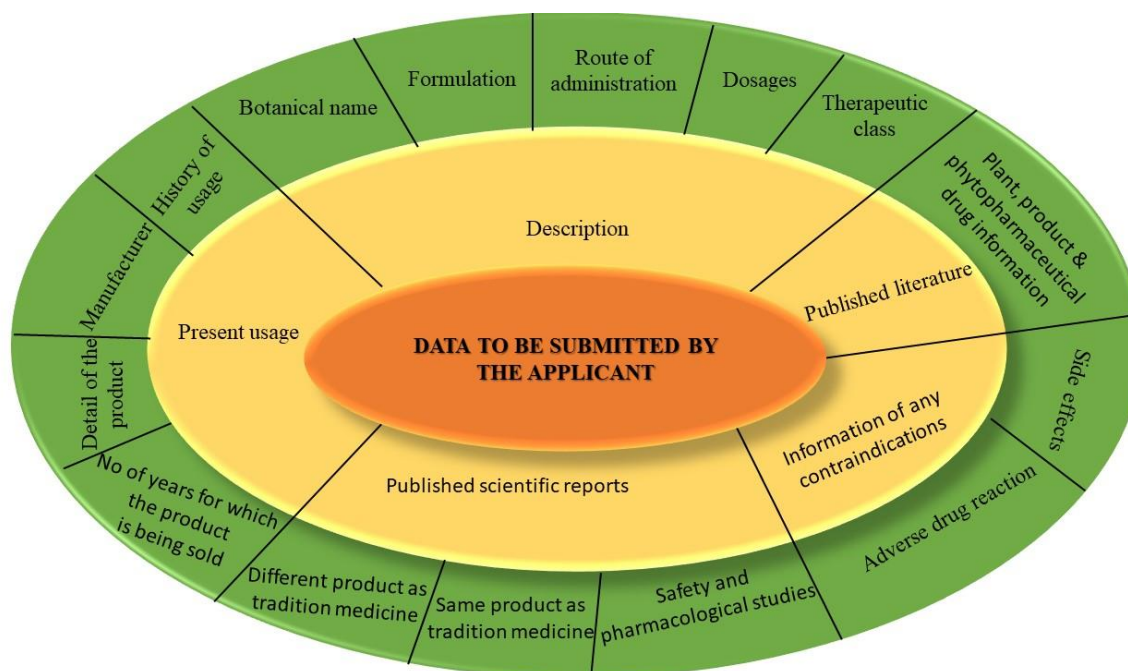


**Figure 1** Development of Phytopharmaceutical drugs

#### 5.1.1. The applicant's data to be submitted

There are also summaries of the phytopharmaceutical medication that include thorough information about the plant, product, or phytopharmaceutical drug, information on any contraindications or adverse effects indicated in traditional medicine or ethnomedicine literature, and reports on the formulation's use. Safety studies on the use of phytopharmaceuticals, including published scientific investigations, are available. Current use of the plant protection drug is to determine the use history, to give information about the product, the manufacturer, the quantity sold, its extent of human exposure and its number of years. Furthermore, mentioned in Figure 2.





**Figure 2** Data to be submitted by the applicant

#### 5.1.2. Information on pharmacology in humans or in clinical settings

According to reports published by the government, there are pharmacological reports including human studies, clinical studies, or epidemiological studies, which are relevant to the pharmaceuticals with health benefits for which a plant-based medication is developed.

#### 5.1.3. Identification, authentication and source of plant used for extraction and fractionation

Medicinal plant preparation is an important first step in undertaking quality research. It entails the extraction and quantification of bioactive constituents prior to conducting the intended biological testing. There are various parameters for identification, authentication and source of plant used for extraction such as:

- Taxonomic classification of the plant that provided the phytopharmaceutical drug.
- Morphological and anatomical description giving diagnostic features and a photograph of plant for further confirmation of identity and authenticity.
- The source of the plant with its geographical location and season or time of collection.
- Every manufacturer and vendor's full list of information, including their name and addresses, on the following things: location where raw materials are harvested, the growing conditions, the various stages of plant growth at harvest, the harvesting time, the storage conditions, and sieving of powdered plant material to obtain uniform particle size.
- Proper quality control for herbal products' efficacy and safety is critical. Because drugs can be described based on several other factors besides their identities, such as purity, content, and other chemicals, physical or biological properties, or manufacturing processes, it is possible to define them. A total ash of not more than 10% and foreign matter less than 20% is one way to ensure a well-manufactured product.
- An agreement to supply a specimen model of a plant that has been labelled and an identity confirmation certificate issued by a certified taxonomist, as well as drawings or photographs of the diagnostic morphological and histological features of the botanical staple that will be used to verify the authenticity of the botanical staple.

#### 5.1.4. Process for extraction and subsequent fractionation and purification

Before extracting any desired natural products, the extraction process is the first step. According to the extraction principle, extraction methods include solvent extraction, distillation, pressing, and sublimation. The solvent extraction method is the most frequently used.

- Quality standards and test methods are considered for starting material.
- Following relevant processing details should be specified, such as solvent selection, extractive values, solvent residue tests, chemical tests, microbial loads, and heavy metal contaminants; and additional information on excipients, diluents, stabilisers, and preservatives should be provided. chemical compound characterization via a chromatographic fingerprinting technique, which includes the use of a phytochemical reference marker and a test for the compound's main active constituent.

#### 5.1.5. Formulation and Manufacturing process of phytopharmaceutical drug

Ayurvedic formulation is a dosage form containing one or with multiple herbs or herbs that have been processed in specified quantities to supply a wide range of therapeutic, nutritional, and cosmetic benefits. Extraction, distillation, expression, fractionation, purification, concentration, or fermentation are all methods used to extract Ayurvedic preparations from botanical constituents. One of the most difficult tasks is to objectively evaluate contradicting toxicological, epidemiological, and other data. In phytopharmaceutical drug formulation, the subsequent details should be mentioned such as; composition, test for identification of phytopharmaceutical drug, the proportion of final purified fraction with a defined marker of phytopharmaceutical drug per unit dose, name, and proportion of all excipient, stabilizers, and any other agent used and packaging material. Active and inactive phytopharmaceutical chromatographic fingerprint profile (FPPCh) is a quality specification for active and inactive phytopharmaceutical chromatographic fingerprint profile with phytochemical reference. The environmental controls, together with the manufacturing method, in-process quality control tests, and the limit of acceptance, are all part of the method of manufacture of the dosage form. Packaging material, packaging steps, and a description of the final pack should also be included if the material being processed does not meet its specifications. Numerous quality specifications for finished products are provided; these include tests specific to the dosage form, a chromatographic fingerprint profile with a phytochemical reference marker, and an assay for the active constituent or a characteristic marker, if an active constituent is unknown.

#### 5.1.6. Current Good Manufacturing Practice (GMP) requirements to manufacture phytopharmaceutical drugs

The Drug and Cosmetic (D&C) Rules Schedule M has the manufacturer's normal good manufacturing practise (GMP) requirement for the manufactured drug. The condition depends on the ingredients and on the processing stages. When applied, the idea is that raw herb (cultivation/collection/drying/minimal processing/storage and transport) GMP requirements will be met across the chain. Additionally, formulation of botanical materials will be done, however, presently, there is no finalised GMP guideline for Phytopharmaceutical drugs. Future applicants would need to follow these procedures and documentation to prevent contamination, degradation, and to preserve the final phytopharmaceutical's standard and integrity.

#### 5.1.7. Stability data

Stability testing is critical to the development of plant-based pharmaceuticals. Stability tests conducted by drug regulatory agencies across the world have recommended guidelines. For storage periods of one month, two months, three months, and six months, stability data for the phytopharmaceutical drug in dosage form or formulation should be kept at a temperature of  $40 \pm 2^\circ \text{C}$  and a relative humidity of  $75\% \pm 5\% \text{RH}$  in an environment free of extremes, within the packaging used for marketing.

#### 5.1.8. Safety and pharmacological information

Following the guidelines for the safety and efficacy of herbal medicines, which were developed by an expert committee, it was decided that all traditional and herbal products wishing to enter clinical trials for any therapeutic condition should follow the same procedures as those followed by the Office of the Drug Controller General of India for allopathic drugs. In addition to animal toxicity and safety data, such as 28 to 90 days repeat-dose oral toxicity on two species of animals, in-vitro genotoxic data (Ame's test and Chromosomal aberration test as per Schedule Y), dermal toxicity tests for topical use products, and teratogenicity studies, the information on safety and pharmacological studies must be provided (only if the phytopharmaceutical drug is meant to be used during pregnancy).

#### 5.1.9. Human Studies

It would be necessary to conduct well-conducted clinical trials on phytopharmaceuticals in order to estimate their safety (toxicology) and efficacy on the same lines as synthetic compound-based drugs. Ayurvedic medicines are exempt from such obligatory specifications. An additional requirement, which is not generally known or required for Traditional medicines, is evidence of a possible mechanism. Appendix IB of Schedule Y of D&C Rules sets out additional clinical trials

that should be performed for phytopharmaceutical drugs that are regulated as prescribed by the relevant rules and guidelines. Since the clinical trial is to help determine the most tolerated dose and the associated toxicities, before doing the studies, data and protocols from the trial must be provided. Both preliminary study protocols and data from dose-finding studies performed should be submitted before beginning any study. They need as long as within the case of the phytopharmaceutical drug already marketed for over five years or where there is enough published evidence regarding the phytopharmaceutical drug's safety, the studies is also abbreviated, modified, or relaxed.

#### *5.1.10. Confirmatory clinical trials*

According to applicable rules and guidelines, protocols for any specific or special safety and efficacy studies proposed specifically for the phytopharmaceutical drug should be submitted for approval. Additionally, proposed protocols for human clinical studies appropriate to come up with or validate safety and efficacy data for the phytopharmaceutical dosage form or product should be submitted for approval.

#### *5.1.11. Regulation status*

In Indian regulations, the key of Ayurveda, Siddha, or Unani (ASU) drugs contain:

- The Classical ASU drugs are produced and named according to the formulas described in the authoritative textbooks. Manufacturing licence is not required for this category if only authoritative books and published literature are cited for the given drug. Patent or proprietary medicine uses ingredients found in authoritative texts, but with intellectual intervention, innovation, or invention in order to manufacture distinct products from classical medicine.
- Under the new phytopharmaceuticals regulation, using advanced solvent extraction techniques, fractionation, modern formulation development, and other techniques is now permitted for pharmaceuticals development. The new phytopharmaceutical drug would have its marketing status as a new chemical entity-based drug once NDA approval is received from CDSCO. Phytopharmaceutical regulation is in agreement with similar regulations in the USA, China, and other countries that involve data generation and scientific evaluation. This new regulation is expected to lead to innovations as well as the development of new drugs derived from botanicals and would make it easier for modern medical professionals to accept the use of herbal products. Academia, researchers, and industry would benefit from increased funding for phytopharmaceutical drug development. For instance, in some countries and across all categories, the phytopharmaceutical drug referenced in this entry is known as functional food, dietary supplement, traditional medicine, or an approved drug.

#### *5.1.12. Post Marketing Surveillance*

The process of identifying and collecting data about drugs after they are licenced for use in a large population is known as postmarketing surveillance (PMS). One of the most important roles of PMS could be to systematically evaluate the safety and effectiveness of new drugs all over the world, especially for those patients with a wide range of alternative health problems. In the preapproval stage, the population of people who will eventually use the drug is radically different from the population studied when the drug is released. The first two years after approval, applicants must provide updates every six months for the first two years, and thereafter they are required to submit updates every year.

#### *Abbreviations*

- AYUSH= Ayurveda, Unani, Siddha, Homeopathy,
- CDSCO= Central Drugs Standards Control Organization,
- NDA= New Drug Application,
- GAPs= Good Agricultural Practices,
- GMPs= GOOD Manufacturing Practices,
- CCRAS= Central Council for Research in Ayurvedic Sciences,
- PLIM= Pharmacopoeial Laboratory for Indian Medicine,
- SOP= Standard Operating Procedures,
- INDA= Investigational New Drug Application,
- ASU= Ayurveda, Siddha, or Unani,
- PMS= Post marketing surveillance.

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## 6. Conclusion

Herbal medicine was the oldest and most commonly used medicinal system. For over three thousand years, Indian ayurvedic, siddha, and unani medicinal herbal products have been produced and sold in the country. For the past decade, there has been a rising acceptance of herbal medicinal products throughout the world. They are now both preventive and curative measures for a variety of ailments. Increasing global consumption underscores the necessity of ensuring the provision of quality, safety, and efficacy policies and regulations for herbal medicinal products in order to satisfy the needs of the global population. Herbal medicinal products can be found all over the world and are rising rapidly in both food and pharmaceutical applications. Concern about medicinal plant material and finished herbal formulations is heightened because of the increased global market for herbal products. Herbal products, like other pharmaceuticals, must have quality, safety, and efficacy in order to be effective. With such a limited amount of evidence, reliable and consistent quality approaches, and research on traditional treatment methods, it is no wonder the herbal drug market is confronted with numerous challenges. Lack of regulation, weak quality control systems, and loose distribution channels plague dietary supplements and nutraceuticals that fall under the category of herbal products. Roughly USD 3 billion in India's domestic markets face quality and safety issues as the country becomes the second-largest producer of medicinal plant products. Of the many manufacturing units of which the majority are small and medium-sized, about 8000 of them are still in operation. To keep the standards of herbal remedies, drug regulators in India are putting emphasis on quality, but the manufacturers are struggling with the increased standards for these products. Ayurvedic, Unani, Siddha, and Homeopathy practises in India are facing challenges when it comes to standardisation, completed formulations, and evidence-based practises for the industry.

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## Compliance with ethical standards

### *Acknowledgments*

The authors are thankful to the Sunder Deep Pharmacy College Dasna, Ghaziabad, for providing the necessary facilities.

### *Disclosure of conflict of interest*

The authors declare that they have no conflict of interest.

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