

Review article

Phytopharmaceuticals: A new class of drug in India

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Abstract

With increasing importance of plant based natural product including extracts, enrich fraction, essential oils, phytomolecules, flavors and fragrances attract the pharmaceutical as well as cosmetic industry. Phytopharmaceuticals are the newer class of drug including enrich fraction containing at least four specific chemical markers with one biomarker. This category provides the way forward for the plant based enrich fraction to be used as a drug, which is not a part of Ayurvedic literature. It has been very important to know the chemical composition and quantity of pharmacologically active ingredients in the formulation. The provisions for synthetic drugs are not appropriate or relevant for botanical based products. Taking this point into consideration AYUSH and CDSCO define and set guidelines on preparation of phytopharmaceutical drugs as the need of science-based drug from botanicals of traditional medicine which has a long history but not properly documented. Generally, the herbal drugs are poorly regulated and controlled by the health authorities, so the efforts are made for analytical control and standardization of the component for therapeutically safe medication. This article is aimed to provide specific and compiled knowledge of herbal medicine regulated under AYUSH in contrast to new category phytopharmaceuticals. This new class of drug may encourage the interest and demand of plant-based therapeutics for unmet medical needs professionally as unlike conventional pharmaceuticals (suspect everything); and AYUSH medicines (trust everything), phytopharmaceutical is a balanced approach which trust everything but underlines the revalidation of the specification of the plant material.

Key words: Phytopharmaceutical drug, Traditional system of medicine, AYUSH medicine standardization

1. Introduction

The use of natural product is as old as human civilization and the main sources of drugs are mineral, plant and animal. Traditional medicines are the backbone of phytomedicine or phytopharmaceuticals and about of 365 plants, animals and minerals are reported to be useful as medication from ancient time and as per World Health Organization (WHO) report, about 70% to 95% of citizens in a majority of developing countries still depends on traditional medicine as their primary source of medication. The use of herbal medicine started to decline after the 1960s as large quantities of resources and money were used to promote synthetic medication and their immediate action. Synthetic medications offer fast relief in dose dependent (Mohamed, 2012), however, due to many adverse effects associated with them, herbal medicine gets greater pace in community acceptance of their better therapeutics effects. This field is bringing forward new lead drug discoveries as well as safe and efficacious plant-based medicines. Therefore, plants become a great source of interest in modern system of therapeutics as drugs, nutraceuticals, pharmaceutical intermediates, folk medicines, and

chemical entities for synthetic drugs. In turn, this leads to growing number of sales of commercialized medicinal herbs and most importantly, growing number of pharmaceutical companies that involve in the research and development of plants as a source for modern medicine. Mother nature is already rich in plant drugs. However, shortcomings associated with the products derived from plants, viz., inefficiency (ineffective therapy) and side effects restrict growing interest for the therapeutic use of natural products. This is due to the poor regulation of natural products in India. Authorities dealing with the efficacy and safety procedures feel lack in quality products and hence limited trade and reluctance in prescribing phytomedicinal products (Rates, 2001).

In the new category of drugs, enrich fraction containing at least four specific chemical markers with one biomarker is to be used as a phytopharmaceutical drug and which is not a part of Ayurvedic literature. Phytopharmaceuticals are the plant-based enrich fractions anthocyanidins, carotenoids, lycopenes, flavonoids, glucosinolates, isoflavonoids, limonoids, polyphenols, omega-3 fatty acids, phytoestrogens, having specific pharmacological effects in human health. Many of these substances possess various therapeutic properties against inflammation, allergic, oxidation, microbial infection, diabetes, ageing and many more (Gupta, 2015). This category has become very important as there is steep growth in demand for regulated herbal medicines, knowledge regarding specific chemical composition, quantity of pharmacologically active ingredients and standardization of the herbal formulations. Taking this point into consideration, guidelines regarding the preparation

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of phytopharmaceutical drugs have been set as the growing need of science-based drug from the box of traditional medicine which has a long history of improper documentation.

As formulation and standardization of medicinal plants is necessary to ensure the quality and consistency of the traditional medicinal plant products (Nafiu *et al.*, 2017), this review tries to expound on the importance of phytopharmaceutical medicine in modern drug development by highlighting salient topics from the history of herbal medicine and examining its roles in modern drug development. In addition, this review also discusses the recent rules and regulations of regarding phytopharmaceutical and phytopharmaceutical preparations, standardization, and challenges of the quality of medicinal plant preparations (Mohamed, 2012).

Definitions

Herbal drugs are mainly whole, fragmented or cut, plants, algae, fungi, lichen, in an unprocessed state, usually in dried form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal drugs.

Herbal medicinal products are those medicinal products which, as active substances, solely contain herbal drug preparation, such as comminuted parts of plants, extracts, pressed juice or distillates of plants. Isolated plant constituents such as digitoxin or menthol, as well as homeopathic medicinal products, are not regarded as herbal medicinal products.

Marker substances are chemically defined constituents of herbal drugs, herbal drug preparations and herbal medicinal products which, according to the state of scientific knowledge, do not contribute to the therapeutic activity else only serve analytical purposes.

Drug as per Section 3(b) of D and C act 1940 “Drug” includes all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes. Such substances (other than food) intended to affect the structure or any function of the human body or intended to be used for the destruction of (vermin) or insects which cause disease in human beings or animals, as may be specified from time to time by the Central Government by notification in the official Gazette. All substances intended for use as components of a drug including empty gelatin capsules.

Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

Ayurveda, siddha, 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 Tibb system of medicine, specified in the First Schedule.

Patent or proprietary medicine in relation to Ayurvedic, Siddha or Unani Tibb systems of medicine of all formulations containing only such ingredients mentioned in the formulae described in the authoritative books of Ayurveda, Siddha or Unani Tibb system of medicine specified in the first Schedule but does not include a medicine which is administered by parenteral route and also a formulation included in the authoritative books as specified in clause (a).

Phytopharmaceutical drugs as per D and C act 1940, these include purified and standardized fraction with defined minimum four bio-active or phytochemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include administration by parenteral route.

As per gazette notification dated 24th October, 2013, “Phyto-pharmaceutical drug” includes processed or unprocessed standardized materials derived from plants or parts thereof or combination of parts of plants, extracts or fractions thereof in a dosage form for internal or external use of human beings or animals and intended to be used for diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, but does not include administration by parenteral route”.

New phytopharmaceutical drug as defined in the Act including bulk drug substance which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labelling thereof and has not been recognized as effective and safe by the licensing authority mentioned under rule 21 for the proposed claims:

Clinical trial (Clinical study) is a systematic study of ASU drug/ Patent or Proprietary Medicines on human subjects-(whether patients or non-patient volunteers)-in order to discover or verify the clinical, pharmacological (including pharmacodynamics/ pharmacokinetics), and/or adverse effects, with the object of determining their safety and/or efficacy.

2. Indian system of medicine (ISM)

The Indian System of Medicine is of great antiquity. It is the culmination of Indian thought of medicine which represents a way of healthy living valued with a long and unique cultural history, as also amalgamating the best of influences that came in from contact with other civilizations be it Greece (resulting in Unani Medicine) or Germany (Homeopathy) or our scriptures/sages which gave us the science of Ayurveda, Siddha as also Yoga and Naturopathy. Like the multifaceted culture in our country, traditional medicines have evolved over centuries blessed with a plethora of traditional medicines and practices.

The main objectives of ISM are to promote good health and expand the outreach of health care through ISM, improve the quality of teachers, clinicians and researchers, improve the infrastructural facilities, ensure safe and efficacious use of drugs in ISM, facilitate pharmacopoeial standards of raw material, integrate ISM in health care delivery system and clinical practice, aware public globally for use of herbal products and provide full opportunity for the growth and development of ISM. Traditional healthcare system of India covers all the systems which originated in India and outside but got adopted and adapted in course of time. ISM includes Ayurveda, Homeopathy, Unani, Siddha and Naturopathy.

Ayurveda (900-800 BC)

Ayurveda is the oldest traditional medicinal systems of India that is meant for preventive, promotive and curative healthcare originating from the Vedas. 'Āyu', *i.e.* life and 'veda', *i.e.* knowledge constitute the word 'Ayurveda'. It is being practiced in India as well as other countries worldwide. It is one of the most ancient healthcare systems having equal scientific relevance in the modern world, that take a holistic view of the physical, mental, spiritual and social aspects of human life, health and disease. Numerous references of health, diseases, their treatment as well as use of nonmaterialistic things such as sun rays, fasting, mantra, *etc.*, are available in these Vedas. The knowledge of Ayurveda was first comprehensively documented in the compendia like 'Brahma Samhita', 'Āgnivesha tantra', 'Bhela Samhita', *etc.* Out of these, only some part of Bhela Samhita is available today. The Agnivesha Tantra was edited by Charak around 5000 years back called Charak Samhita and thereafter re-edited by Dridhbala, which is one of the main text of Ayurveda available in complete form today. This is the most translated treatise of Ayurveda, which got translated into many foreign languages like Tibetan, Arabic, Unani and Greek even in ancient time. As per the fundamental basis of Ayurveda, all objects and living bodies are composed of five basic elements, called the Pancha Mahabhootas, namely: Prithvi (earth), Jal (water), Agni (fire), Vayu (air) and Akash (ether). The philosophy of Ayurveda is based on the fundamental correlation between the universe and the man. Hence Ayurveda has also stressed on environmental aspects and has advised various measures for conservation of nature as well as to avoid the pollution of Air, water and Soil. Ayurveda imbibes the humoral theory of Tridosha- the Vata (ether + air), Pitta (fire) and Kapha (earth + water), which are considered as the three physiological entities in living beings responsible for all metabolic functions. The mental characters of human beings are attributable to Satva, Rajas and Tamas, which are the psychological properties of life collectively terms as 'Triguna'. Ayurveda aims to keep structural and functional entities in a state of equilibrium, which signifies good health (Swasthya). Any imbalance due to internal or external factors leads to disease and the treatment consists of restoring the equilibrium through various procedures, regimen, diet, medicines and behavior change. The treatment approach in the Ayurveda system is holistic and individualized having preventive, curative, mitigative, recuperative and rehabilitative aspects. The preventive aspect of Ayurveda is called Svasth-Vritta and includes personal hygiene, daily and seasonal regimens, appropriate social behavior and use of materials & practices for healthy aging and prevention of premature loss of health attribute. The curative treatment consists of Aushadhi (drugs), Ahara (diet) and Vihara (life style). Ayurveda largely uses plants as raw materials for the manufacture of drugs, though materials of animal and marine origin, metals and minerals are also used. Ayurvedic medicines are generally safe and have little or no known adverse side-effects, if manufactured properly and consumed judiciously following the necessary do's and don'ts (AYUSH; Parasuraman *et al.*, 2014).

Siddha (800-700 BC)

The Siddha System of medicine is one of the ancient systems of medicine in India having its close bed with Dravidian culture. The

term Siddha means achievements and Siddhars are those who have achieved perfection in medicine. Eighteen Siddhars are said to have contributed towards the systematic development of this system and recorded their experiences in Tamil language. The Siddha system of Medicine emphasizes on the patient, environment, age, sex, race, habits, mental frame work, habitat, diet, appetite, physical condition, physiological constitution of the diseases for its treatment which is individualistic in nature. Diagnosis of diseases are done through examination of pulse, urine, eyes, study of voice, colour of body, tongue and status of the digestion of individual patients (Vaidya and Devasagayam, 2007). System has unique treasure for the conversion of metals and minerals as drugs and many infective diseases are treated with the medicines containing specially processed mercury, silver, arsenic, lead and atheros without any side effects. The strength of the Siddha system lies in providing very effective therapy in the case of Psoriasis, Rheumatic disorders, Chronic liver disorders, Benign prostate hypertrophy, bleeding piles, peptic ulcer including various kinds of Dermatological disorders of non-psoriatic nature (AYUSH).

Unani (460-377 BC)

Unani system of medicine is a comprehensive medical system, which provides preventive, promotive, curative and rehabilitative health care. The system is holistic in nature and takes into account the whole personality of an individual rather than taking a reductionist approach towards disease. The fundamentals, diagnosis and treatment modalities of the system are based on scientific principles. The basic framework of this system is based on the Hippocratic theory of four Humors, according to which any disturbance in the equilibrium of humors causes disease and therefore the treatment aims at restoring the humoral equilibrium. The system also believes that Medicatrix Naturae is the supreme power, which controls all the physiological functions of the body, provides resistance against diseases and helps in healing naturally. Temperament of a patient is given great importance both in diagnosis and treatment of diseases. It is also taken into consideration for identifying the most suitable diet and lifestyle for promoting the health of a particular individual. The remarkable holism of Unani system of medicine arises from giving primacy to the Temperament of man and drug, which unlike the molecular level, is simple and can be known as a whole. Its ease of practice arises from the fact that it uses only a few parameters, *i.e.*, the primary qualities (Kayfiyat) of Hot: Cold and Dry: Wet to describe the temperament of both man and drug. Unani system of medicine described four mode of treatment viz., Ilaj-bil-Tadbir (Regimenal Therapy), Ilaj-bil-Ghidha (Dietotherapy), Ilaj-bil-Dawa (Pharmacotherapy) and Ilaj-bil-Yad (Surgery) (Kalim *et al.*, 2010). The thrust areas of Unani medicine include; skin diseases, liver disorders, noncommunicable diseases including life style diseases, metabolic and geriatric diseases and menstrual / gynaecological disorders, *etc.* It has the methods of understanding and maintaining health in a positive and individualized manner with different guidelines for different temperaments, genders, age groups, geographical regions, seasons, occupations, *etc.* In Unani System of Medicine, drugs obtained only from herbal, animal and mineral sources are used for medication. Sometimes, these drugs are used singly, and sometimes in the form of a compound of various drugs. They may be subjected to physico-chemical processing but without breaking up their natural character (AYUSH; Kalim *et al.*, 2010).

Homeopathy (1850 AD)

“Homoeopathy” was introduced as a scientific system of drug therapeutics by a German Physician, Dr. Christian Frederick Samuel Hahnemann in 1805. While translating a medical treatise by Scottish physician and chemist, William Cullen, from English to German, in 1790, he came across a foot note under Cinchona that attributed its fever curing property to the astringent (decongestant) qualities of the drug. Being athos of Cullen’s remarks concerning the effect of Cinchona for curing malaria, Hahnemann experimented its effect on himself by taking repeated doses of cinchona tincture and experienced fever, shivering and joint pains: symptoms similar to those of malarial fever. After series of experiments, Hahnemann concluded that a drug that could produce certain symptoms in healthy individuals could also cure similar disease symptoms, in accordance with some hidden, natural laws of athos as had been vaguely perceived by ancient physicians. This led to the coining of the word “homoeo-pathy” (which comes from the Greek: hómoios, “like” and athos, “suffering”). Based on this, Hahnemann postulated the key principle of Homoeopathy, the Law of Similars, logically evolving it as an experimental science, according to the method of inductive reasoning after exact observation, correct interpretation, rational explanation and scientific construction (AYUSH; Poitevin, 1999).

Naturopathy

Naturopathy is rooted in the healing wisdom of many cultures and times based on principal of natural healing. The principles and practices of Naturopathy are integrated in the life style, if the people observe living close to nature. Naturopathy is a cost effective drugless, non-invasive therapy involving the use of natural materials for health care and healthy living (Fleming and Gutknecht, 2010). It is based on the theories of vitality, boosting the self-healing capacity of the body and the principles of healthy living. Naturopathy is a system of natural treatment and also a way of life widely practiced, globally accepted and recognized for health preservation and management of illnesses without medicines. Naturopathy advocates living in harmony with constructive principles of Nature on the physical, mental, social and spiritual planes. It has great promotive, preventive, curative as well as restorative potentials. Naturopathy promotes healing by stimulating the body’s inherent power to regain health with the help of five elements of nature - Earth, Water, Air, Fire and Ether. It is a call to “Return to Nature” and to resort to a simple way of living in harmony with the self, society and environment. Naturopathy advocates ‘Better Health without Medicines’. It is reported to be effective in chronic, allergic autoimmune and stress related disorders. The theory and practice of Naturopathy are based on a holistic view point with particular attention to simple eating and living habits, adoption of purificatory measures, use of hydrotherapy, cold packs, mud packs, baths, massages, fasting (AYUSH; Elder, 2013), *etc.*

Botanicals constitute a major portion of ISM. For example, Indian Materia Medica includes about 2000 drugs of plant origin. About 1250 Indian medicinal plants are used as therapeutic formulations in ISM and about 85% of ISM preparations are poly-herbal. However, therapeutic, and phytochemical validation and metabolomic studies, chemo profiling for quality control and standardization of these herbal medicines are done to ensure new drug application. Chemo profiling is done to control quality by marker analysis using HPLC/

HPLC-MS/GC/GC-MS. By this way we quantify bioactive compounds, find spurious drug, compare fingerprint of pure with adulterated and substituted drug, standardize herbal drugs, check stability of drugs under storage condition and quality.

3. Regulation of herbal drugs

Globally, herbal medicine has been considered an important alternative to modern allopathic medicine. Although the herbal medicines are very popular in the society, only few medicinal herbs have been scientifically evaluated for their potential in medical treatment. In most countries, the herbal drugs are poorly regulated and are often neither registered nor controlled by the health authorities. The safety of herbal medicines remains a major concern. In the United States, the Food and Drug Administration (FDA) has estimated that over 50,000 adverse events are caused by botanical and other dietary supplements. In addition, for most herbal drugs, the efficacy is not proved and the quality is not assured. The World Health Organization’s (WHO) Traditional Medicine (TM) Strategy 2014-2023 focuses on promoting the safety, efficacy, and quality of TM by expanding the knowledge base and providing guidance on regulatory and quality assurance standards. By 2012, about 119 WHO member states have their own regulation for herbal medicines (Bhatt, 2016).

Acts administered in the ISM sector

- Central Council of Indian Medicine Act-1973
- Central Council of Homoeopathy Act-1973
- Drugs and Cosmetics Act-1940 and Rules there under
- Drugs and Magic Remedies Act-1954, 1955 and Rules there under
- Medicinal and Toiletries Preparation acts and Rules-1995-96

The regulatory scenario regarding herbal preparations varies from country to country. Globally, several diverse regulatory approaches are in vogue such as they use same regulatory requirements for all products, with certain types of evidence (unusual for herbal medicines) and exemption of herbal medicines for any regulatory requirement concerning registration or marketing authorization.

3.1 Problems with regulated herbal products

As herbal drugs are not uniformly regulated and are poorly documented, there could be many reasons behind this. Herbal medicines are generally considered as safe. However, herbal drugs are not always safe as they are promoted. The assumption that everything that is natural is safe not correct. This is due to the quality related safety issues and it needs information of primary processing and quality specifications. The following issues are need to be addressed for fully regulated herbal medicines.

- Quality control
- Safety of the herbal preparations
- Development of effective marker
- Clinical efficacy of marker
- Documentation
- Regulatory harmonization

3.2 General regulatory requirements for NDA of different class of herbal medicines

FDA Botanical Drug Development Guidance describes appropriate development plans for botanical drugs to be submitted in new drug applications (NDAs) and specific recommendations on submitting investigational new drug applications (INDs). The term botanical means products that include plant materials, algae, macroscopic fungi, and combinations thereof. FDA guidance recommends that IND must contain sufficient information to demonstrate that the drug is safe for testing in humans and that the clinical protocol is properly designed for its intended objectives (Bhatt, 2016).

In addition to general regulatory requirements for an NDA-nonclinical pharmacology/toxicology studies, clinical evidence of efficacy and safety-for botanical drugs there are special requirements to ensure safety and quality of botanicals as follows:

Description of product and documentation of prior human experience

- Description of botanical raw materials used and known active constituents or chemical constituents
- Prior human experience

Quality control

- Botanical raw materials
- Botanical drug substance and drug product: Identity, chemical characterization, manufacturing processes, biological assay, specifications, stability, current good manufacturing practices, and environmental assessment

Evidence to ensure therapeutic consistency

- Botanical raw material control
- Quality control by chemical test (s) and manufacturing control
- Biological assay
- Clinical data: Dose-response data and multiple batch clinical data

4. Regulation of herbal drugs in India

In Indian regulations, the major class of Ayurveda, Siddha, or Unani (ASU) drugs included are:

- 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. For this category, 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.
- Patent or proprietary medicine makes use of ingredients referred to in the formulations of authoritative texts but with intellectual intervention, innovation, or invention to manufacture products different from the classical medicine. For this category, issue of a license to manufacture requires proof of effectiveness, based on the pilot study as per relevant protocol for ASU drugs.

4.1 Restrictions prevailing under AYUSH system

- All ingredients have to be listed in the books of Schedule I of DCA.
- Separated group of secondary metabolites / purified isolates are not permitted.
- Blending of botanicals with vitamins / synthetic substances is not permitted.
- Botanicals of foreign origin cannot be used.
- Several modern dosage forms are not permitted.
- Only some of pharmaceutical excipients are allowed.
- Standardization by adjusting the amounts of specific constituents is not permitted.
- Therapeutic pluralism?

A separate Department of Indian Systems of Medicine and Homoeopathy (ISM and H) was set up in 1995 to ensure the optimal development and propagation of ASU systems of healthcare. The Department of ISM and H was re-named as the Department of Ayurveda, Unani, Siddha, and Homeopathy (AYUSH) in November 2003. In 2010, AYUSH introduced Rule 158 (B) which made the requirement of proof of effectiveness for licensing of a patent or proprietary ASU medicine. This was followed by the release of GCP guidelines for voluntary use by the researchers interested in taking up clinical trials using ASU medicine. In India, ASU drugs have been under the purview of Department of AYUSH (AYUSH Guidelines, 2013).

5. Phytopharmaceutical

In contrast to AYUSH regulation, 2015 regulatory requirements for phytopharmaceuticals are under the purview of the Central Drugs Standards Control Organization (CDSCO). This gazette notification defines regulatory provisions for phytopharmaceuticals and regulatory submission requirements for scientific data on quality, safety, and efficacy to evaluate and permit marketing for an herbal drug on similar lines to synthetic, chemical moieties. When conventional pharmaceuticals suspect everything, AYUSH medicines that trust everything, phytopharmaceutical is a balanced approach which trust everything but underlines the revalidation of the specification of the plant material.

Phytopharmaceutical drug is defined as purified and standardized fraction with defined minimum four bioactive or phytochemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation, or prevention of any disease or disorder but does not include administration by parenteral route (Gazette, 2015).

In Schedule Y, the newly added Appendix I B describes data to be submitted along with the application to conduct clinical trial or import or manufacture of a phytopharmaceutical drug in the country. The regulatory requirements for NDA for the phytopharmaceutical drug include standard requirements for a new drug-safety and pharmacological information, human studies, and confirmatory clinical trials (Gazette, 2015). For phytopharmaceutical drug, there is a lot of stress on:

Available information on the plant, formulation and route of administration, dosages, therapeutic class for which it is indicated

and the claims to be made for the phytopharmaceutical, and supportive information from published literature on safety and efficacy and human or clinical pharmacology information

Data generated on:

- Identification, authentication, and source of the plant used for extraction and fractionation.
- Process for extraction and subsequent fractionation and purification.
- Formulation details of phytopharmaceutical drug.
- Manufacturing process of formulation.
- Stability data.

The new phytopharmaceuticals regulation permits the development of the drug development using advanced techniques of solvent extraction, fractionation, potentiating steps, modern formulation development, *etc.* After NDA approval from CDSCO, the marketing status of the new phytopharmaceutical drug would be like that of a new chemical entity-based drug. The new regulation for phytopharmaceutical is in line with regulations in USA, China, and other countries involving scientific evaluation and data generation. This new regulation is expected to 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. It would encourage research in phytopharmaceutical drug development for academia, researchers, and industry (Narayana and Katiyar, 2013).

The Government of India has published a draft amendment to Drugs and Cosmetics Act, and Rules (D and C Act and Rules) on 24th October 2013. This creates regulatory provisions of defining phytopharmaceuticals (botanical based drugs) and a schedule providing requirements of scientific data on quality, safety, and efficacy to evaluate and marketing authorization for a plant-based lead as a drug on similar lines to synthetic, chemical moieties. In India, it is known that though the new draft regulation was not present, Guggulu tablets (for treatment of hypercholesterolemia), Ginkgo-biloba tablets (to treat temporary loss of memory), and Silymarin capsules (to treat liver disorders) have been approved and marked as drugs by the Central Drugs Standards Control Organization (Drug Controller General of India). However, it is known that approval of Guggulu tablets took a more than a decade to get this approval as a drug. It had required efforts to convince the authorities that several requirements applicable to a synthetic chemical were not possible for a botanical-based product. There is a need for development of science-based drugs from botanicals especially from the basket of traditional knowledge (namely Ayurveda), which has a long history of safety and use documented in the authoritative books. The authors are not the first people to have felt this need for separate and appropriate regulatory provisions for botanicals as drugs. In fact, US Food and Drug Administration (FDA) has published a document titled "Guidance to Industry for Botanical Drugs" in June 2004. It is also known that US FDA has issued a marketing authorization to a topical cream containing standardized green tea extract as a US botanical for treating genital warts after evaluating the respective Investigational New Drug Application scientifically. The authors believe that India should have had taken leadership in a similar way (Narayana and Katiyar, 2013).

Government of India appointed a committee for this purpose in August 2008. The committee was chaired by Dr Nitya Anand and Dr. D.B.A. Narayana served as a convener. Professor S.S. Handa, Professor R.H. Singh, Dr C.K. Katiyar, Dr. Amit Agarwal, and Dr. G.N. Singh were the members of the expert committee. Several eminent leaders of the pharmaceutical industry and pharmacists who delivered their annual presidential addresses to the Indian Pharmaceutical Congress, which is held annually since the last 64 years, talked about the need to develop botanical drugs from leads inspired by Ayurvedic wisdom. However, in order to remove potential confusions amongst Ayurvedic fraternity about the amendments, we stress the need to recognize various aspects covered below:

- The above draft regulations are under Chapter IV of D and C Act and Rules, and hence related to synthetic drug-based products.
- Ayurveda, Siddha, and Unani (ASU) drugs are regulated under Chapter IVA of D & C Act and Rules, and hence, the above draft regulations do not have any impact on the way ASU product is currently regulated. Those who wish to continue to manufacture and sell ASU drugs under the current ASU licensing system of ASU preparations (as per classical texts) or proprietary Ayurvedic medicines are allowed under law can do so.
- The above draft regulations are also not a 'mandatory' provision that applies to ASU drugs in any way.

5.1 Standardization of phytopharmaceutical

Primary processing information is done by checking harvest location, growth conditions, stage of plant growth at harvest, harvesting time, checking collection, washing, drying and storage conditions, way of handling, garbling, transportation, grinding, pulverization of the plant material, sieving for getting uniform particle size of powdered plant material followed by authentication of plant material, presence of phytotoxins, foreign matter, volatile matter, radioactive contaminants checking organoleptic evaluation, macroscopy and microscopy, ash values, solvent residues, microbial count, heavy metal residues, pesticide residues, mycotoxin residues, chromatographic profiles, assay of "bio active"/marker compounds and successive extractive values (Yadav *et al.*, 2009).

5.2 Definition of standardized phytopharmaceutical

As per Indian Pharmacopoeia, 2014, standardized extract means an extract adjusted within an acceptable tolerance to a given content of biomarker or chemical/analytical marker. Standardization may be achieved by adjusting the extracts with approved inert material or by blending one or more batches of extracts.

As per USP, Dietary Supplements Compendium, 2012, standardized ingredients contain a defined amount of a particular chemical constituent or group(s) of constituents known as marker compound (s). A complete definition of standardization includes the information and controls needed to produce a material of predetermined and defined consistency.

As per European Pharmacopoeia, standardization means the adjusting of the herbal drug preparation to a defined content of a constituent or a group of substances with known therapeutic activity, respectively by adding excipients or by blending herbal drugs or herbal preparations.

5.3 Integrated approach for selection of phytopharmaceutical

This selection can be based on traditional knowledge, modern literature, from experience, bioassays, cost/availability of supply chains, biodiversity/threat status, international regulatory status and variability in chemistry/stability.

5.4 Salient features about phytopharmaceuticals

Phytopharmaceuticals can be from a botanical origin and can be from any part of the globe. Its proposal is in line with regulations in USA, China, and other countries involving scientific evaluation and data generation. It does not simply depend on traditional knowledge alone. Phytopharmaceutical's proposal would promote innovations and development of new drugs from botanicals in a scientific way and would give encourage to research in drug development for innovators, industry, and national laboratories and pharmaceutical research labs in India. Phytopharmaceuticals as proposed above permits development as a drug under chapter IV of D and C Rules, adopting the drug development technologies involving modern techniques of solvent extraction, fractionation, potentiating steps, add-back techniques, modern extraction techniques (like CO₂ based extraction), freeze-drying, formulation developments, and many other techniques. Stress on high degree of characterization of the plant-based ingredient as a phytopharmaceutical is a requirement that is not generally asked for any traditional medicine (TM). Ayurvedic drugs are regulated differently and need to meet the requirements given in authoritative texts recognized in the schedule and also have to be processed using methods given in such texts. The leads for phytopharmaceuticals can have their origin not only in TMs like ASU, Traditional Chinese Medicine, Kambo Medicine, Bhutanese Medicines or from Ethnobotany, tribal medical practices, and other such sources. Most nations are already putting regulations for access and benefit sharing in such cases and exploitation will not be going unregulated. Phytopharmaceuticals would need to be mandatorily evaluated for safety (toxicology) and efficacy through well-conducted human clinical trials on lines similar to synthetic compound-based drugs. Such mandatory requirements do not apply to Ayurvedic medicines. Information on possible mechanism of action also is a requirement, not generally known or required for TMs. Phytopharmaceuticals when approved by Drug Controller General of India would have the same status for marketing as that given for a synthetic compound-based drug. The committee that prepared these draft regulations approved by Drug Technical Advisory Board (DTAB) - the statutory body under the drugs law to advise the central government on technical matters relating to drug - has recommended that products licensed under these regulations may be allowed to be prescribed by both Bachelor of Medicine, Bachelor of Surgery (MBBS) and Bachelor of Ayurvedic Medicine and Surgery (BAMS) qualified physicians (Narayana and Katiyar, 2013).

We feel that this new class of drugs would encourage introduction of extensive evaluation through biomedical sciences, therefore would help in the acceptance of and expand the use of herbal products by modern medical profession. Across the world, there is a rising interest and demand for plants as a possible source of therapeutics for unmet medical needs, and this step would bring this aspiration one step closer to reality. Upon finalization of this regulation, which we feel need to be done as soon as possible, number of national

laboratories in India, scientists groups, and industrial research and developments (R and Ds) who have been working on botanical leads can look forward to take this route for getting marketing permissions. New entrants/investors will get encouraged to invest in this route for drug development.

5.5 Key limitations associated with phytopharmaceutical

- Small and Medium Enterprise generally do not find it cost effective to develop phytopharmaceuticals.
- Clinical trials, international patents and product registration in the international markets are the two major cost components which require financial support.
- Due to lack of a regulatory system, very little scientific work has happened which can lead to development of rational, evidence based, phytopharmaceuticals.
- Unfriendly patent related regulations and systems are also becoming a hindrance.
- The Biological Diversity Act 2002 also impacts the present and future of phytopharmaceuticals in a significant way.

5.6 Requirements for the submission of application to conduct clinical trial or import or manufacture of a phytopharmaceutical drug in the country

PART - I

Data to be submitted by the applicant

- A brief description or summary of the phytopharmaceutical drug (botanical name of the plant including vernacular or scriptural name), formulation and route of administration, dosages, therapeutic class for which it is indicated and the claims to be made for the phytopharmaceutical product.
- Published literature including information on plant or product or phytopharmaceutical drug, as a traditional medicine or as an ethnomedicine and provide reference to books and other documents, regarding composition, process prescribed, dose or method of usage, proportion of the active ingredients in such traditional preparations per dose or per day's consumption and uses.
- Information on any contraindications, side effects mentioned in traditional medicine or ethno-medicine literature or reports on current usage of the formulation.
- Published scientific reports in respect of safety and pharmacological studies relevant for the phytopharmaceutical drug intended to be marketed:
 - (a) Where the process and usages are similar or same to the product known in traditional medicine or ethnomedicine; and
 - (b) Where process or usage is different from that known in traditional medicine or ethnomedicine.
- Information on any contraindications, side effects mentioned or reported in any of the studies, information on side effects and adverse reactions reported during current usage of the phytopharmaceutical in the last three years, wherever applicable.

- Present usage of the phytopharmaceutical drug to establish history of usages, provide details of the product, manufacturer, quantum sold, extent of exposure on human population and number of years for which the product is being sold.

Human or clinical pharmacology information

- Published scientific reports in respect of pharmacological studies including human studies or clinical studies or epidemiological studies, relevant for the phytopharmaceutical drug intended to be marketed.
 - (a) Where the process and usages are similar or same to the product known in traditional medicine or ethnomedicine; and
 - (b) Where process or usage is different from that known in traditional medicine or ethnomedicine.
- Pharmacodynamic information (if available).
- Monographs, if any, published on the plant or product or extract or phytopharmaceutical. (Copies of all publications, along with English translation to be attached).

PART – II

Data generated by applicant

- Identification, authentication and source of plant used for extraction and fractionation:
 - (a) Taxonomical identity of the plant used as a source of the phytopharmaceutical drug giving botanical name of genus, species and family, followed by the authority citation (taxonomist's name who named the species), the variety or the cultivar (if any) needs to be mentioned.
 - (b) Morphological and anatomical description giving diagnostic features and a photograph of the plant or plant part for further confirmation of identity and authenticity. Furnish certificate of confirmation of botanical identity by a qualified taxonomist.
 - (c) Natural habitat and geographical distribution of the plant and also mention whether the part of the plant used is renewable or destructive and the source whether cultivated or wild.
 - (d) Season or time of collection.
 - (e) Source of the plant including its geographical location and season or time of collection.
 - (f) A statement indicating whether the species is any of the following, namely;
 - Determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered species (CITES) of wild Fauna and Flora;
 - Entitled to special protection under the Biological Diversity Act, 2002 (18 of 2003);
 - Any known genotypic, chemotypic and ecotypic variability of species.
 - A list of grower or supplier (including names and addresses) and information on the following items for each grower or supplier, if available or identified already, including information of primary processing, namely;

- (a) Harvest location;
 - (b) Growth conditions;
 - (c) Stage of plant growth at harvest;
 - (d) Harvesting time;
 - (e) Collection, washing, drying and storage conditions;
 - (f) Handling, garbling and transportation;
 - (g) Grinding, pulverising of the plant material; and
 - (h) Sieving for getting uniform particle size of powdered plant material.
- Quality specifications, namely;
 - (a) Foreign matter
 - (b) Total ash
 - (c) Acid insoluble ash
 - (d) Pesticide residue
 - (e) Heavy metal contamination
 - (f) Microbial load
 - (g) Chromatographic finger print profile with phytochemical reference marker
 - (h) Assay for bioactive or phytochemical compounds
 - (i) Chromatographic fingerprint of a sample as per test method given under quality control of the phytopharmaceutical drug (photo documentation).
 - An undertaking to supply specimen sample of plant duly labeled and photocopy of the certificate of identity confirmation issued by a qualified taxonomist along with drawings or photographs of the diagnostic morphological and histological features of the botanical raw material used for the confirmation of authenticity.
 - Process for extraction and subsequent fractionation and purification:
 - (a) Quality specifications and test methods for starting material.
 - (b) Steps involved in processing.
 - Details of solvent used, extractive values, solvent residue tests or limits, physicochemical tests, microbial loads, heavy metal contaminants, chromatographic finger print profile with phytochemical reference markers, assay for active constituents or characteristic markers, if active constituents are not known;
 - Characterization of final purified fraction;
 - Data on bioactive constituent of final purified fraction;
 - Information on any excipients or diluents or stabilizer or preservative used, if any.
 - Details of packaging of the purified and characterized final product, storage conditions and labeling.
 - Formulation of phytopharmaceutical drug applied for:
 - (a) Details of the composition, proportion of the final purified fraction with defined markers of phytopharmaceutical drug per unit dose, name and proportions of all excipients, stabilizers and any other agent used and packaging materials.

- (b) Test for identification for the phytopharmaceutical drug.
 - (c) Quality specifications for active and inactive phytopharmaceutical chromatographic finger print profile with phytochemical reference marker and assay of active constituent or characteristic chemical marker.
 - Manufacturing process of formulation:
 - The outline of the method of manufacture of the dosage form, along with environmental controls, in-process quality control tests and limits for acceptance.
 - Details of all packaging materials used, packing steps and description of the final packs.
 - Finished product's quality specifications, including tests specific for the dosage form, quality and chromatographic finger print profile with phytochemical reference marker and assay for active constituent or characteristic marker, if active constituents are not known.
 - Stability data:
 - (a) Stability data of the phytopharmaceutical drug described at 4 above, stored at room temperature at 40 +/- 2 deg. C and humidity at 75% RH +/- 5% RH for 0,1, 2, 3 and 6 months.
 - (b) Stability data of the phytopharmaceutical drug in dosage form or formulation stored at room temperature at 40 +/- 2 deg. C and humidity at 75% RH +/- 5% RH for 0, 1, 2, 3 and 6 months, in the pack intended for marketing.
 - Safety and pharmacological information:
 - (a) Data on safety and pharmacological studies to be provided.
 - (b) Animal toxicity and safety data.
 - 28 to 90 days repeat dose oral toxicity on two species of animals;
 - *In vitro* genotoxicity data (Ame's test and Chromosomal aberration test as per Schedule Y);
 - Dermal toxicity tests for topical use products;
 - Teratogenicity study (only if phytopharmaceutical drug is intended for use during pregnancy);
 - Human studies:
 - (a) Clinical trials for phytopharmaceutical drugs to be conducted as per applicable rules and guidelines for new drugs.
 - (b) For all phytopharmaceutical drugs data from phase I (to determine maximum tolerated dose and associated toxicities) and the protocols shall be submitted prior to performing the studies.
 - (c) Data of results of dose finding studies performed and the protocols shall be submitted prior to performing the studies: Provided that in the case of phytopharmaceutical drug already marketed for more than five years or where there is adequate published evidence regarding the safety of the phytopharmaceutical drug, the studies may be abbreviated, modified or relaxed.
 - Confirmatory clinical trials:
 - (a) Submit protocols for approval for any specific or special safety and efficacy study proposed specific to the phytopharmaceutical drug.
 - (b) Submit proposed protocol for approval for human clinical studies appropriate to generate or validate safety and efficacy data for the phytopharmaceutical dosage form or product as per applicable rules and guidelines.
 - (c) Submit information on how the quality of the formulation would be maintained during the above studies.
 - Regulatory status: Status of the phytopharmaceutical drug marketed in any country under any category like functional food or dietary supplement or as traditional medicine or as an approved drug.
 - Marketing information:
 - (a) Details of package insert or patient information sheet of the phytopharmaceutical drug to be marketed.
 - (b) Draft of the text for label and carton.
 - Post marketing surveillance (PMS):
 - (a) The applicant shall furnish periodic safety update reports every six months for the first two years after approval the drug is granted.
 - (b) For subsequent two years the periodic safety update reports need to be submitted annually.
 - Any other relevant information: Any other relevant information which the applicant.
- ## 6. Application of phytopharmaceuticals
- Phytopharmaceuticals are refer to a group of natural substances that include anthocyanidins, carotenoids, lycopenes, flavonoids, glucosinolates, isoflavonoids, limonoids, polyphenols, omega3 fatty acids, phytoestrogens, resveratrol, phytosterols, probiotics and terpenoids with specific pharmacological effects in human body. Some of them are summarized below:
- ### Carotenoids
- The most common examples of carotenoids are α -carotene, β -carotene, lycopene, lutein, and zeaxanthin. Some of them such as β -carotene, lycopene, lutein and zeaxanthin have been reported to be in reverse to the risk of cardiovascular diseases, some kinds of cancers and eye disorders. However, lutein has various kinds of therapeutic effects and protects against uterine, prostate, breast, colorectal and lung cancers. It also protects gastro intestinal cancer. Carotenoids have antioxidant properties by which they show their beneficial effects (Gupta, 2015).
- ### Lycopene
- It is class of carotenoids but deficient in pro-vitamin A activity. It is present in various fruits and vegetables. Intake of lycopene rich dietary food items like tomatoes and products thereof is associated with lowering in the chance of chronic disorders like cancer and cardiovascular diseases. Increase in serum and tissue lycopene levels decreases the risk of various chronic diseases (Gupta, 2015).
- ### Flavonoids
- Flavonoids are polyphenolic compounds which are usually obtained in fruits and vegetables like berries, legumes, tea, grapes, olive oil, cocoa, walnuts, peanuts, spices, fruits, and green vegetables, onion, apple, berries and tea. These are reported to be active against various

bacterial disease, oxidation, viral diseases and algesia. Bunch of flavonoids are the plant phenols and ketones such as flavanones, dihydroflavonols, flavones and flavanols. Quercetin and kaempferol are the other flavonoids which are generally present at relatively low concentrations 12-28 mg/kg of fresh plant weight. Flavanols are usually obtained in onions, leeks, broccoli and blueberries. Flavonoids are reported to be active against free radicals; free radical mediated cellular signaling, inflammation, allergies, platelet aggregation, microbes, ulcers, viruses, tumors and hepatotoxins (Panche *et al.*, 2016).

Limonoids

Limonoids are present in citrus fruits as major source of terpenoids. These are highly oxygenated tri-terpenoids with substantial anticancer actions. d-limonene is the commonest monocyclic monoterpene, found in orange peel oil and inhibits pancreatic cancer (Suntar *et al.*, 2018).

Terpenoids

These are also known as isoprenoids. These are the largest class of phyto-nutrients in green foods and grains. These are obtained from mosses, liverworts, algae and lichens, as well as in insects, microbes or marine organisms. These are required to fix carbon through photosynthetic reactions using photosensitizing pigments. Animals have evolved to utilize these compounds for hormonal and growth regulatory functions. The presence of these molecules in animal tissues also provides a measure of protection from certain diseases (Singh and Sharma, 2015).

Omega-3 fatty acids

There is extensive interest in increasing consumption of omega-3 fatty acids because they are associated with many health benefits. The main food sources of the long chain omega-3 fatty acids are fish, especially fatty species such as salmon, rainbow trout, mackerel, herring and sardines. Some plants, mainly canola, soybean and flax oils provide the 18-carbon omega-3 fatty acid, alpha-linolenic acid. The benefit of omega-3 fatty acids in the treatment of people suffering from osteoarthritis is well known. In people who have osteoarthritis, increased consumption of omega-3 fatty acids and adequate intake of monounsaturated fatty acids such as those found in olive oil (and reduced consumption of omega-6 fatty acids) can improve symptoms and even sometimes allow a reduction in the use of nonsteroidal anti-inflammatory drugs (NSAIDs). One strategy to increase the availability of long-chain omega-3 fatty acids is to develop oilseed crops such as canola and soybean that contain stearidonic acid. This omega-3 fatty acid occurs naturally in only a few plants such as black currant seed oil and echium oil (Bradberry and Hilleman, 2013).

Phytoestrogens

Phytoestrogens are non-steroidal phytochemicals quite similar in structure and function to gonadal estrogen hormone. They offer an attractive alternate for hormone replacement therapy (HRT) with beneficial effects on cardiovascular system and may even alleviate menopausal symptoms. They are potential alternatives to the synthetic selective estrogen receptor modulators, which are currently applied in HRT. On the basis of chemical structure, phytoestrogens can be classified as flavonoids, isoflavonoids, coumestans, stilbenes and lignans. They occur in either plants or

their seeds. Soybean is rich in isoflavones, whereas the soy sprout is a potent source of coumestrol, the major coumestan. The highest concentrations of coumestans are found in clover and soybean sprouts (Rietjens *et al.*, 2017).

Resveratrol

It is a natural phytoalexin which is made by the plants in stress conditions and pathogen attack. It is produced after various physiological effects. At lower dose which is normally intake by food, resveratrol has been reported to exert neuroprotective and cardioprotective effects. This is due to its antioxidant properties. It is recognized for its widespread therapeutic actions like anti-thrombogenic, anti-inflammatory, cardioprotective, neuroprotective, antiageing and anticancer. Resveratrol is found in considerable concentrations in grapes, peanuts, *etc.* (Keylor *et al.*, 2015).

Phytosterols

These are defined as plant sterols and plant stanols. Phytosterols lower total and blood cholesterol level by preventing cholesterol absorption from the intestine. Phytosterols are naturally found in fruits, vegetables, nuts and principally oils. Market demand for phytosterol-fortified products is expected to increase in near future as the growth rate of cardiovascular disease is being increased in India. There is no doubt that phytosterol as a functional food ingredient will be a new approach to reduce cholesterol level and hold a great promise for long term health management (Lin *et al.*, 2016).

Synbiotics (Probiotics and prebiotics)

The concept of using a prebiotic and probiotic in a synergistic relationship to increase the relative number of beneficial bacteria in the gut is a new and promising area of investigation. Synbiotic is the combination of a prebiotic and a probiotic in which the prebiotic is used to increase the intestinal survival of the probiotic. They are used as an aid in the treatment of inflammatory diseases affecting the intestinal tract, such as inflammatory bowel disease and other syndromes. In addition, synbiotics are frequently recommended after a course of antibiotics as a means of restoring the microbiota within the intestinal tract to its normal, healthy state, as well as an aid in resolving uncomplicated cases of diarrhoea. They modify the composition of the microbiota of the gastrointestinal tract, restore the microbial balance and therefore have the potential to provide health benefits. The majority of probiotic microorganisms belong to the genera *Lactobacillus* and *Bifidobacterium* (Markowiak and Elisewska, 2017).

7. Conclusion

The new phytopharmaceuticals regulation encourages and permits the development of plant-based drugs using advanced techniques of solvent extraction, fractionation, potentiating steps, modern formulation development, *etc.* After NDA approval from CDSCO, the sponsor can market this new phytopharmaceutical as a new chemical entity-based drug. The new regulation for phytopharmaceutical is in line with regulations in U.S., China and other countries involving scientific evaluation and data generation. This is expected to promote innovations and development of new drugs from botanicals under the modern medicine framework. It would encourage research and will attract investment in phytopharmaceutical drug development for academia, researchers and industry.

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Conflict of interest

We declare that we have no conflict of interest. However, **Zulfa Nooreen and Vineet Kumar Rai have equal contribution.**

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