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Short Communication

Opportunities and Challenges in Development of Phytopharmaceutical Drug in India- A SWOT Analysis

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ABSTRACT

Background: India had issued a set of regulation for new class of plant based drug 'Phytopharmaceutical drug' as an amendment to the Drugs and Cosmetic Rules 1945. Age old traditional systems of medicine practiced in India 'Ayurveda', 'Siddha' and 'Unani' medicines. Ayurvedic, Siddha or Unani drugs include all medicines in accordance with the authoritative books of Ayurvedic, Siddha and Unani tibb. systems of medicine specified in the first Schedule of Drugs and Cosmetics Act 1940. **Objective:** The article aims to analyse opportunities and challenges in development of phytopharmaceutical drug in India through SWOT analysis. **Methods:** The Strength, Weakness, Opportunities and Threats (SWOT) in development of phytopharmaceutical drug in India was analysed through review of published literatures. **Observation:** The SWOT analysis showed that India being leader in the herbal industry has massive opportunity in national and international market for phytopharmaceutical drug. It was also observed that the phytopharmaceutical drug market has vital opportunity for expansion both in developed and developing countries. **Conclusion:** There is a need for investment and commitment in promoting research and development in the area of phytopharmaceutical drug.

Key words: Phytopharmaceutical drug, SWOT, Drugs and Cosmetics rules, Opportunity, Challenges.

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INTRODUCTION

Treatments using herbal medicines are one of the important forms of traditional medicine and 70% to 80% of the world population prefers this as primary health care.[1] India being pioneer in plant based traditional system of medicine had issued a set of regulation for new class of plant based drug 'Phytopharmaceutical drug'.[2] "Phytopharmaceutical drug" includes purified and standard fraction with defined minimum four bio-active or phyto-chemical compound (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 specified in Rule 2 (eb) of the Drugs and Cosmetics (D and C) Rules, 1945.[2]

USFDA regulates herbal drugs as 'botanicals',[3] 'traditional medicinal product' by EU,[4] 'Traditional products' by Malaysia,[5] 'Traditionally used herbal products' by Philippines,[6] 'Herbal Medicines and Related Products' by Nigeria,[7] 'Traditional products' by Saudi Arabia,[8] 'Complementary medicine' by Australia[9] and as 'Herbal remedies and traditional medicines' by Canada.[10,11] Traditional system of medicine practiced in India is one of the old and well-established systems in the world and it includes 'Ayurveda', 'Siddha' and 'Unani' medicines.[12] 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 authoritative books of Ayurvedic, Siddha and Unani tibb. Systems of medicine specified in the first Schedule of Drugs and Cosmetics Act, 1940. Phytopharmaceutical drugs are the fraction of crude extract and are distinctly differentiated by being purified and standardized.[2] This article aims to analyse Strength, Weakness, Opportunities and Threats (SWOT) in development of phytopharmaceutical drug in India, which helps the readers in understanding better and deeper perspectives in this area of drugs.

STRENGTH

Medicinal plants have been a great source to treat various diseases from the ancient times. Over 4000 years plants were used as a medicine by Unani Hakims, Indian Vaids and reference are available for use of herbs in European and Mediterranean cultures.[13] Ayurveda, Siddha and Unani, Homeopathy medical systems are found mentioned even in the ancient Vedas and other scriptures, about 8,000 herbal remedies are available through AYUSH systems in INDIA. In 5000-1000 BC, four vedas were considered as the oldest Indian literature contains information about natural remedies. Further, Charaka Samhita (focussing on internal medicine) and Susruta Samhita (focussing on surgery) are the considered as classical text of Ayurveda.[14] The extracts of various plants and their parts have also been used as folk medicine as evidenced by Wealth of India to treat various diseases.[15] India has rich source of herbs and serves as a repository of medicinal plants because of its biodiversity.

In recent years, use of herbal medicines has been increasing popular because of the failure of modern therapies against chronic diseases and because of their unwanted significant side effects. Various modern drugs and their synthetic analogues have been prepared from prototype compounds isolated and discovered from plants, few examples are L-Dopa from *Mucuna prurita* and paclitaxel from *Taxus brevifolia*, Reserpine from *Rauvolfia serpentine*, Vincristine and Vinblastine from *Catharanthus roseus.*[16] There are plenty of literatures available for potential

therapeutic use of isolates from plants, standardized extracts derived from *Commiphora guggul* and *Zingiber officinale* are few examples representing phytopharmaceutical class of drugs which are prescribed by physicians and available in Indian market.[17,18] Table 1 showed the list of few phytopharmaceuticals and their therapeutic benefits.[19-38]

India has a well-established long history of safe and continuous use of many herbal drugs and phytopharmaceuticals through officially recognized alternative systems of health *viz*. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy.[39] It has huge potential for herbal drugs due to availability of resources in terms of 1) availability of herbs and herbal products, 2) plenty of literatures like various pharmacopoeias-Indian Pharmacopoeia, Ayurvedic Pharmacopoeia of India, Unani Pharmacopoeia etc which prescribes quality standards for herbs and formulations used in traditional system of medicine, Indian Medicinal plants published by ICMR, huge volumes of scientific literatures, Ancient literatures etc., 3) Experts (physician and scientist) and expertise in the area. In 2013, Government of India had notified a new set of regulations for 'Phytopharmaceutical drugs' as an amendment to the Drugs and Cosmetic Rules 1945, which defines and outlines the regulatory requirements for phytopharmaceutical drugs in India. This gazetted notification regulates the definition, regulatory provisions for phytopharmaceutical drugs and submission requirements including scientific data on quality, safety and efficacy to evaluate and permit marketing for an herbal drug on similar lines to synthetic, chemical moieties. Appendix 1B in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 describes the rules to conduct clinical trials or import/manufacture of Phytopharmaceutical drugs in the country which include the basic information, pharmacognostic data, processing of extract/Phytopharmaceutical, formulation, its stability, safety, toxicity data and human or clinical pharmacology information.[40] India, being known for wealth of herbal medicine led the Global regulatory system by regulating phytopharmaceutical drugs; in Table 2 authors have compared phytopharmaceutical drugs regulation of India with herbal medicine regulations in developed and developing countries, as there is no separate regulation for phytopharmaceutical drugs in other countries.

Table 1: The list of few phytopharmaceuticals and their therapeutic benefits.[19-38]

S. No.	Phytochemical	Botanical name	Therapeutic uses
1	Atropine	*Atropa belladonna*	Impaired memory retrieval[19]
2	Caffeine	*Coffea arabica, Camellia sinensis*	CNS stimulant, decreased tonic immobility[20]
3	Cocaine	*Erythroxylum coca*	CNS stimulant[21]
4	Bilobalide and Ginkgolides	*Ginkgo biloba*	Dementia, age-related cognitive impairment[22]
5	Monoterpenoids and Sesquiterpenes	*Melissa officinalis*	Dementia, cognitive impairment[23]
6	Ginsenosides	*Panax ginseng.*	Cognitive performance[24]
7	Podophyllotoxin	*Podophyllum peltatum*	Anticancer[25]
8	Artemisinin	*Artemisia annua*	Anti-malarial[26]
9	Digoxin	*Digitalis lanata*	Cardiotonic[27]
10	(L)-dopa	*Mucuna pruriens*	Parkinsonism[28]
11	Diosgenin	*Dioscorea deltoidea*	Antiproliferative[29]
12	Morphine	*Papaver somniferum*	Analgesic[30]
13	Colchicine	*Colchicum autumnale*	Anti-tumour[31]
14	Quinine	*Cinchona ledgeriana*	Anti-malarial[32]
15	Silymarin	*Silybum marianum*	Hepatic disorders[33]
16	Ajmaline	*Rauwolfia serpentina*	Antiarrhythmic[34]
17	Berberine	*Berberis vulgaris*	Antidiarrheal[35]
18	Ephedrine	*Ephedra sinica*	Antiasthmatics[36]
19	Ementine	*Carapichea ipecacuanha*	Antiprotozoal[37]
20	Vincristine, Vinblastine	*Catharanthus roseus*	Antitumor[38]

Food and Agriculture Organisation, United Nations had estimated that the worldwide trade volume for plant extracts was about 1 Trillion USD in 2003/04 with an expected annual growth rates of 6% to 8% worldwide. The world market in 2011 for Phytopharmaceuticals was 100 billion USD and in Europe it was about 32 billion Euro[43] (2014). Market demand for phytopharmaceuticals in India and for Indian products world-wide will be growing day by day.

WEAKNESS

Tremendous increase in the use of herbal medicine was observed over past two decades, but still there is a significant lack of research data in this field. There is a need for creating awareness among health professionals and scientists about the need of quality and evidenced based research and archival of scientific data, this will help in developing evidence based phytopharmaceutical drug.

Increase in demand for phytopharmaceutical drugs in global market may lead to compromise in quality due to adulteration and substitution, which will become the greatest threat for health of consumers.[44-46] Availability and identification of quality phytopharmaceuticals is the major challenge for the regulatory authorities, as adulteration and mis-identification of raw material for phytopharmaceutical drug may occur due to confusion from vernacular names and inter-species variation in various geographical conditions.[46-49] Need for robust method for identification of raw material at field during collection. Figure 1 detail the steps involved in manufacturing of phytopharmaceutical drugs and challenges involved.

Traditional systems of medicines are practiced as per the standards like Ayurvedic pharmacopoeia, Siddha Pharmacopoeia, Unani pharmacopoeia etc and through available ancient literatures. These systems involve medicinal plants in some or the other forms but there is lack of interrelation or coordination between them, which may lead to increase in cost of treatment.

OPPORTUNITIES

Opportunities in phytopharmaceuticals are massive because of its increasing demand to fulfil the purposes of therapeutic used as well as nutritional dietary supplements. As India is a bio-diverse country in terms of flora medicinal plant cultivation and export of plant material

Table 2: Comparison of Phytopharmaceutical drug regulation in USA, EU and India.[40-43]

S.No	Parameters	US[42]	EU[43]	India[40]
1	Phytopharmaceutical drug regulation	Not available	Not available	Available
2	Other related regulations	Botanicals	Traditional medicinal product	Ayurveda, Siddha, Unani, Homeopathy
3	Definition	Botanicals mean products that include plant materials, algae, macroscopic fungi and combinations thereof	Any medicinal product, exclusively containing as active ingredients one or more herbal substances/herbal preparations, or a combination of the two	Phytopharmaceutical drug includes purified and standard fraction with defined minimum four bio-active or phyto-chemical compound (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 specified in Rule 2 (eb) of the Drugs and Cosmetics Rules, 1945
4	Regulatory authority	United States Food and Drugs Administration	European Medicines Agency	Phytopharmaceutical Drug: Central Drugs Standards Control Organisation
5	Regulatory pathways			Ayurveda, Siddha, Unani, Homeopathy: AYUSH
6	Legislation and Regulation	Dietary supplement Health and Education Act 1994 for marketing authorisation, non-clinical studies, clinical trials and efficacy.	Directive 2001/83/EC and Directive 2001/82/EC	Phytopharmaceutical Drug: GSR 918 (E), Amendment in Drugs and Cosmetics Rules 2015 Ayurveda, Siddha, Unani, Homeopathy: Drugs and Cosmetics Act 1940 and Rules thereunder
		Data to be generated and submitted by applicant		
7	Certificate of identity from taxonomist	√		√
8	Taxonomical identification of source plant	√	As per European Pharmacopoeia	√
9	Morphological and anatomical identification of source plant/part	√		√
10	Geographical distribution	√	√	√
11	Season/time of collection	√	√	√
12	Information with respect to Endangered Species Act; Biological Diversity act, 2002; genotypic, chemotypic and ecotypic variability of species	√	X	√
13	List of grower/supplier	√	√	√
14	Quality specifications (foreign matter, total ash, acid insoluble ash, pesticide residue, heavy metal contamination, microbial load, chromatographic fingerprint for sample and marker, assay for bio-active compound)	√	As per European Pharmacopoeia	√
15	Details on Process for extraction, fractionation and purification	√	√	√

Table 2: Cont'd

S.No	Parameters	US[42]	EU[43]	India[40]
16	Details on Packaging, storage condition and labelling	√	√	√
		Data to be generated and submitted by applicant		
17	Details on phytopharmaceutical drug formulation	X	X	√
18	Manufacturing of formulation	X	X	√
19	Stability data of phytopharmaceutical drug and dosage form	ICH Q1A (R2) Stability Testing of New Drug Substances and Products.	'Note for guidance on stability testing of new active substances and products' 'Guideline on stability testing of new veterinary drug substances and medicinal products' 'Guideline on stability testing of existing active substances and related finished products' 'Note for guidance on in-use stability testing of human medicinal products' 'Note for guidance on in-use stability testing of veterinary medicinal products (excluding immunological veterinary medicinal products)	Temperature at 40 ± 2°C and Humidity at 75% RH ± 5% RH for 0,1,2,3 and 6 months. ICH Q1A (R2) Stability Testing of New Drug Substances and Products.
20	Data safety and pharmacological studies	Pharmacokinetic/ Pharmacodynamics Studies and Route of administration	Toxicity studies-Reproductive Genotoxicity, Carcinogenetic and Toxicokinetic data	Systemic Toxicity Studies (14-, 28-, 90- or 180- day), Male Fertility Study, Female Reproduction and Developmental studies, Toxicity Studies, Local toxicity, Allergenicity/ Hypersensitivity, Genotoxicity, Carcinogenicity
21	Animal toxicity study data	Toxicity studies- General, Target organ and system, Reproductive genotoxicity and Carcinogenetic study	Toxicity studies-Reproductive Genotoxicity, Carcinogenetic and Toxicokinetic data	28-90 days repeat dose oral toxicity on two species of animals; *In-vitro* genotoxicity data; dermal toxicity test data for topical use product; teratogenicity study (if applicable)
22	Human studies	Phase 1 tolerability studies may not be required if sponsors can provide adequate justification for the relevance of the prior human use. Phase-2 and Phase-3 studies is conducted	Phase I, phase II, phase III and phase IV studies for safety and efficacy	Clinical trial from Phase 1 to Phase 4, Relaxed or modified, if phytopharmaceutical drug already in market for more than 5 years
23	Information on Regulatory status in other countries	X	X	√
24	Marketing information	No separate guideline	No separate guideline	Information on Package insert of patient information leaflet and label
25	Post marketing surveillance	Submission of PMC and PMRs periodic reports every month	Clinical safety information through Pharmacovigilance and PSURs	PSUR every 6 month for first 2 years and annually for subsequent years
26	Pharmacopoeial Standards	US Pharmacopoeia	European Pharmacopoeia	Indian Pharmacopoeia: for source material

can be done to raise the economy. Increasing demand in herbal industry gives rise to clinical and research opportunities because therapeutic potential of many herbs is yet to be fully discovered. The annual revenue stream from the three major Indian traditional medicinal systems i.e., Ayurveda, Unani and Siddha, is estimated at more than half a billion dollars annually.[50] Moreover, herbal business generates employment opportunities to many people including farmers, local people, industry people, researchers and many more. The projected market for herbal medicines by 2023 is $ 111 billion,[51] which may became an impressive market for phytopharmaceuticals due to availability/confidence of scientific data, it can outclass the herbal and allopathic industry market.

In India 90% of the herbal drug raw material are harvested from wild source and from varying geographical distribution.[52] Correct identification and quality assurance of the starting material is an essential requirement in

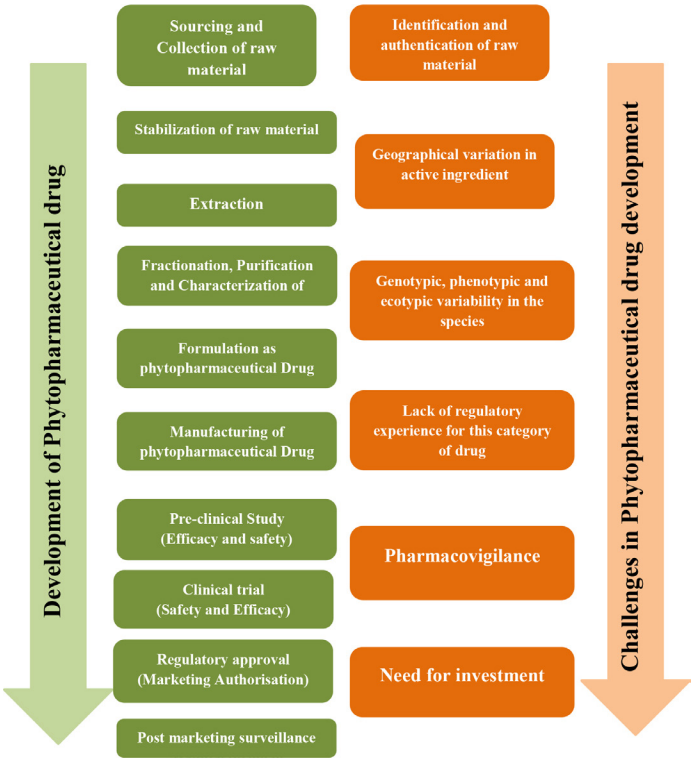

Figure 1: Steps involved in the development of phytopharmaceutical drug and its Challenges.

production of phytopharmaceuticals to ensure its reproducible quality, in turn which contributes to its safety and efficacy. For proper standardization of herbal drugs and phytopharmaceuticals, most of the regulatory guidelines and pharmacopoeias suggest macroscopic and microscopic evaluation and chemical profiling of the botanical materials for quality control.[53-55] Pharmacopoeia,[56-58] a compendial body in the country provides standards for quality control of phytopharmaceuticals through monographs. Indian Pharmacopoeia plays a major role in correct identification of raw materials for traditional system of medicine and by providing quality standards for phytopharmaceuticals.

Development of novel well validated and robust method by combining suitable biotechniques such as transcriptome analysis or Single Nucleotide Polymorphisms (SNP) and Raman spectroscopy methods may be a reliable method for error-free, rapid identification of raw material at the area of collection or further processing for phytopharmaceutical drug development. The combination method will be beneficial in identifying product fidelity, species substitution or adulteration. Adaptation of suitable combination method by regulatory authorities and compendia bodies will improve the quality of phytopharmaceutical drug.

THREAT

Overexploitation of forests is the main threat to many valuable medicinal plants.[59] Rapid increase in population, pollution, modern civilization and industrialization, invasion of exotic species that compete with native species and unsustainable use of natural resources are the main reasons for degradation of plant biodiversity. In South India, it is estimated that about 70-80 out of the estimated 300 medicinal plants are either endangered or threatened.[60] Thus conservation of plant biodiversity and their sustainable use can help to save the future of medicinal plants. In addition, cultivation of financially profitable crops is lucrative for cultivators in comparison to medicinal plant cultivation. On the other hand, increasing global competition along with poor government regulation and management enable others to take lead in the international market like US patented for curcumin isolated from *Curcuma longa*, a native plant of India, for wound healing.[61] But the overall pattern, approach and devotion to the goal will help overcome any such potential threat.

CONCLUSION

The phytopharmaceutical drug market has vital opportunity for expansion both in developed and developing countries. The SWOT analysis showed that India being leader in the herbal industry have massive opportunity in national and international market for phytopharmaceutical drug, however there is a need for investment and commitment in promoting research and development in the area of phytopharmaceutical drugs. The current situations are favouring the growth of phytopharmaceutical industry, provided by adhering to the new set of regulations and by fully exploiting the available opportunities.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

SWOT: Strength, Weakness, Opportunity and Threats; **AYUSH:** Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy; **ICMR:** Indian Council of Medical Research; **CDSCO:** Central Drugs Standard Control Organization.

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