Plant to phytopharmaceutical: The journey and future directions

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Abstract

Nature has an answer for all human needs. Since the beginning of human life, plants have been used as medicines, and these continue to be a valuable reservoir of therapeutic agents and pharmaceutical products. The journey of a plant from nature to the market involves selection, collection, authentication, extraction or isolation of bioactives, chemoprofiling, biological evaluation, and quality assurance. This article highlights the importance of each step and emphasises the need for a sustainable use of plants and incorporating new technologies in order to ensure a regular supply as well as quality, efficacy, and safety of plant products and phytopharmaceuticals.

Keywords: medicinal plants, phytopharmaceuticals, sustainable use, upgrading technology

1. Introduction

Nature has an answer for all human needs: clean air, food, shelter (timber), clothing (fibres), flavours, fragrances, and medicines. Since the beginning of human life, human beings have turned to nature to satisfy all needs. Plants have been used for nutrition and as medicines, and these continue to be a valuable reservoir of therapeutic agents and pharmaceutical products. People use different systems of medicines across the globe (Figure 1). In all systems of medicines, plants are an important reservoir of medicinal products as well as pharmaceutical aids.

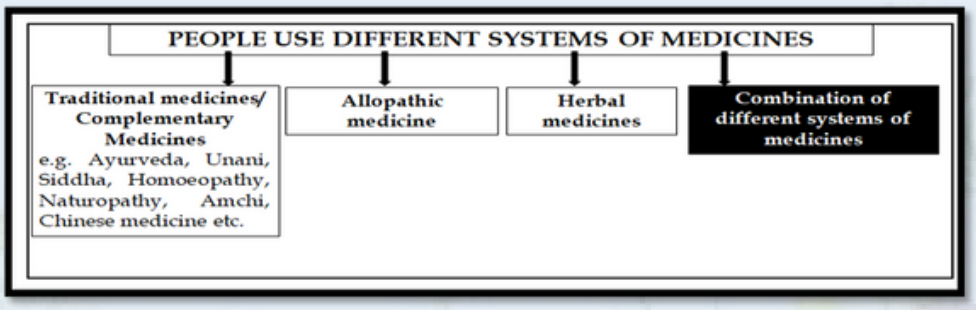


Figure 1. Different systems of medicine

Natural products (and their derivatives and analogues) represent over 50% of all drugs in clinical use in modern medicine. The World Health Organisation estimates that 80% of the people in developing countries of the world rely on traditional medicine for their primary health care, and about 85% of traditional medicine involves the use of plants or plant extracts. This means that more than 4 billion people in the world rely on medicinal plants as sources of drugs (1).

In the world of medicine, natural products are popular as:

- Pharmaceutical products (Therapeutic agents, Pharmaceutical aids, Models for drug discovery, For semi-synthesis of important drugs)
- Nutraceuticals
- Cosmetics/ cosmeceuticals
- Bio-pesticides
- Ethno-veterinary products

Plant-based traditional medicines, complementary therapies, and herbal medicines are extremely popular, not only in the developing countries but also in the 'developed nations', especially for chronic ailments. It is pertinent to mention that the world-wide trade of medicinal plants has been growing exponentially with an annual growth rate of 15%; it is likely to touch a scale of five trillion US dollars by 2050. The importance of plants in pharmacy cannot be overemphasised. Hence, it is imperative to understand the journey of a plant to a commercial product.

2. Journey of a plant to a phytopharmaceutical product: The steps

Plants are used in various forms and commercially a variety of formulations containing medicinal plants/ products are available commercially. The marketed preparations used in different systems of medicine contain plants or plant extracts or isolated phytoconstituents (figure 2). In layperson's words, these are phytopharmaceuticals medicines or therapeutic products obtained from plants and plant products.

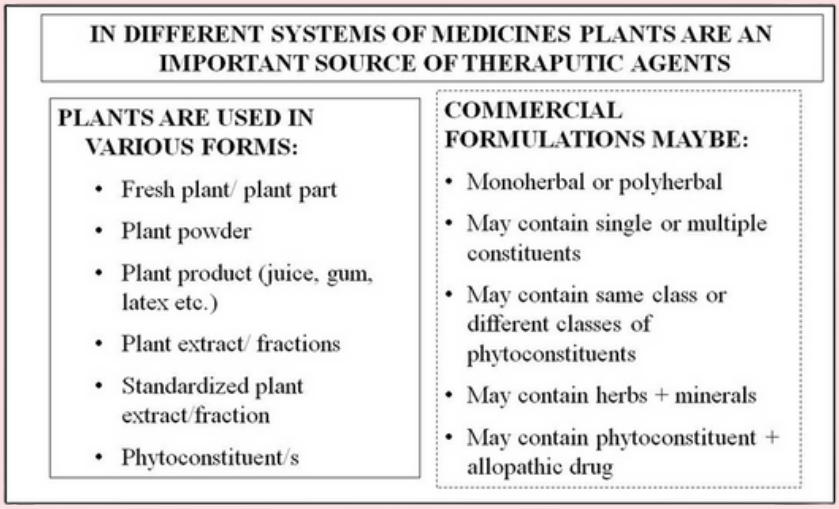


Figure 2. Different forms in which plants are used in various systems of medicine

As per the Drugs & Cosmetics (D&C) Rules, 1945, "Phytopharmaceutical drug" includes a purified and standard fraction with defined minimum four markers (bioactive or analytical that are determined qualitatively and quantitatively) in 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 (2). For developing reliable a phytopharmaceutical product, correct identity, purity, quality, efficacy, safety stability must be determined (3). The overview of the steps involved in developing a commercial plant product in figure 3 (4).

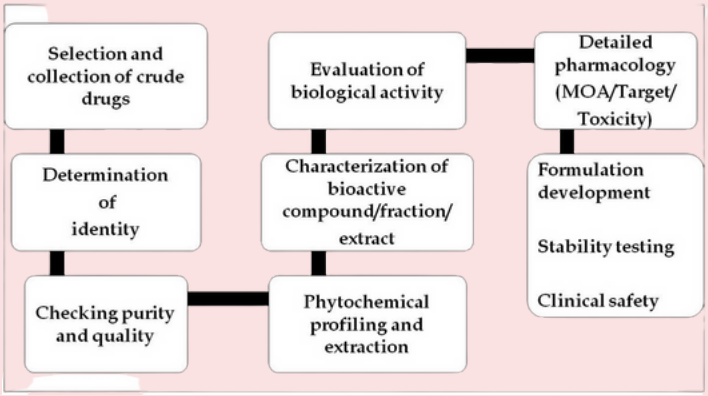


Figure 3. Steps involved in developing a commercial plant product

The steps for developing a plant product are discussed below:

2.1. Selection of plant

The rationale for selection of a plant must be clearly stated. The selection maybe ethno-guided based on traditional uses, based on field observations, chemotaxonomy driven, and based on type of reported phytoconstituents.

2.2. Procurement/collection of selected plant

Medicinal plants are procured from wild or cultivated sources. These have their advantages and limitations (Figure 3). In our country about 6,000-7,000 species are used in Indian systems of medicine and folk medicines. Of 960 species in trade, 178 species have an annual consumption > 100 MT. Only about 20% of these are obtained by cultivation (5).

	WILD SOURCES	CULTIVATED SOURCES
ADVANTAGES	•Easy access •Wide variety •Higher amount of secondary metabolites	•Regular supply •Greater uniformity •Known quality
LIMITATIONS	○Incorrect identification ○VARIATION ○NO REGULAR SUPPLY ○INDISCRIMNATE UTILIZATION (plants become vulnerable, threatened, endangered, extinct)	○More expensive ○Agrotechnology for large majority of Medicinal plants needs to be developed ○Knowledge transfer from research institutes is required. (Farmers reluctant to leave cultivation of known crops)

Figure 3. Advantages and limitations of wild and cultivated sources of crude drugs

Collection of raw material may be done from either source and to ensure reproducibility the place of collection-wild or cultivated, time/month and year of collection, plant part collected, method for drying (natural/artificial) must be documented. For standardization studies the plant should be collected from different geographical regions in different seasons and the various parameters should be examined.

2.3. Authentication of the collected material

For any industry, selecting the right raw material is the key to the process of making a quality product. In the journey of developing a phytopharmaceutical, authentication i.e. determination of the correct identity of the plant of interest is critical. If the plant material is wrong the entire process will be wasted (Figure 4).

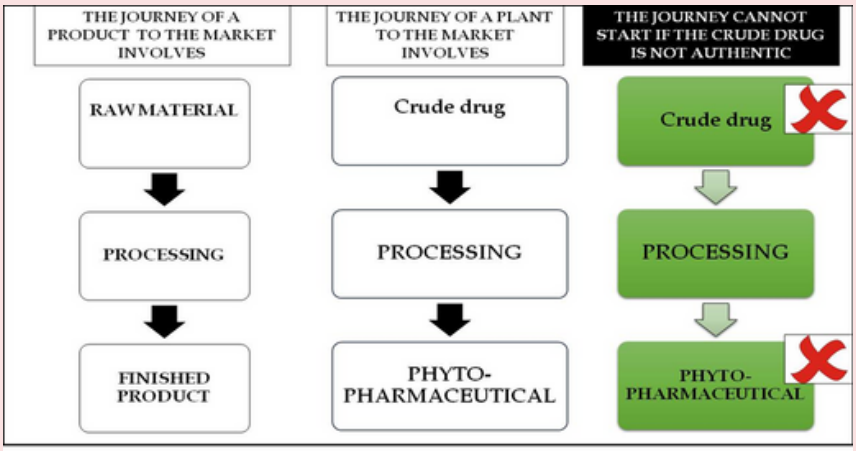


Figure 4. The importance of authentication of plants in herbal drug industry

Authenticating the plants may be done by taxonomists (especially for plants for which information is not available) or by studying the organoleptic features, microscopic features (including transverse section, powder microscopy and histochemistry and quantitative determination), physicochemical parameters of the plant (including foreign organic matter, moisture content, ash values, extractive

values swelling index, pesticide residues, microbial contamination, presence of heavy metals etc.). These results are compared with available literature to confirm the identity.

2.4. Preparation of extracts

Plants contain diverse constituents - primary and secondary metabolites as well as active and inert materials. The objective of preparing a plant extract is to separate the phytoconstituents which are responsible for the plant's activity. Figure 5 summarizes the general sequence employed for extraction.

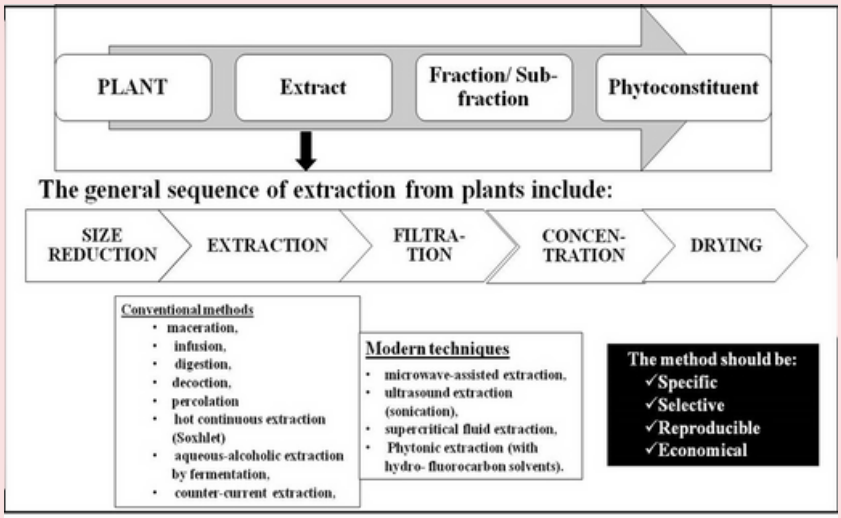


Figure 5. General sequence for preparing plant extract

To ensure reproducibility the method of size reduction of plant material, amount of plant material, crude drug : solvent ratio, and method of extraction should be recorded. Extraction should be exhaustive and for a new investigation it is preferable to prepare sequential extracts i.e. starting from non-polar going to medium polar and polar solvents. Method of extraction, duration of extraction and the conditions during extraction should be documented. For example: Maceration with methanol: water (80:20) for 7 days. Solvent replaced after every 48hours; in a shaking incubator at 37°C at 100RPM. At the end of 7 days the extracts to be pooled and concentrated under vacuum.

This is followed by phytochemical screening of the prepared extracts and quantification of the major/ target phytoconstituents (e.g. total alkaloid content; total flavonoid content) along with development of their TLC profiles. Subsequently fractionation of extracts (by solvent partitioning and /or chromatography) is done with a view to isolate bioactive fraction / constituent. Each step for fractionation/isolation should be recorded with all conditions. After that phytochemical profiling and chromatographic fingerprinting of fractions/sub-fractions and characterisation of isolated constituent/s is necessary.

2.5. Once the extracts are ready the question is: WHAT TO DO NEXT?

For pharmacognosists there are a number of options available. Most frequently two approaches are used in Figure 6.

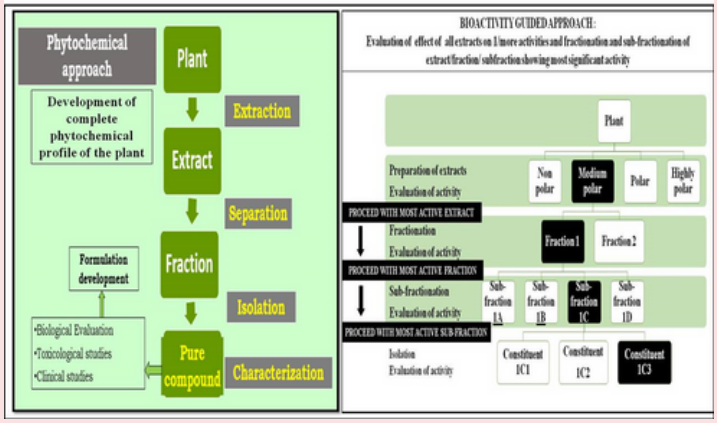


Figure 6. Different approaches to study plants

- **Phytochemical study of test extracts:** This involves separation, characterization and quantification of all secondary metabolites with a view to develop an exhaustive chemo-profile of the plant. This is followed by evaluation of bioactivity.
- **Bioactivity guided study of test extracts:** In this approach for studying plants the focus is on a particular activity. Various extracts are prepared and this is followed by evaluation of effect of all extracts on 1/more activities and fractionation and sub-fractionation of extract/fraction/sub-fraction showing most significant activity. The most active extract/ fraction/constituent is then chemo-profiled/characterized.

It is necessary to mention that in plants a particular activity may be due to one phytoconstituent or due to synergistic effect of a number of constituents. Thus while examining a plant one should understand that the bioactive component may be a single compound or a fraction or an extract.

2.6. Biological evaluation of the prepared extracts

The selected plant may have support of traditional literature or maybe used in folklore medicine; some plants may have preliminary pharmacological proof and some may have no evidence at all. Hence they have to be examined accordingly (Figure 7).

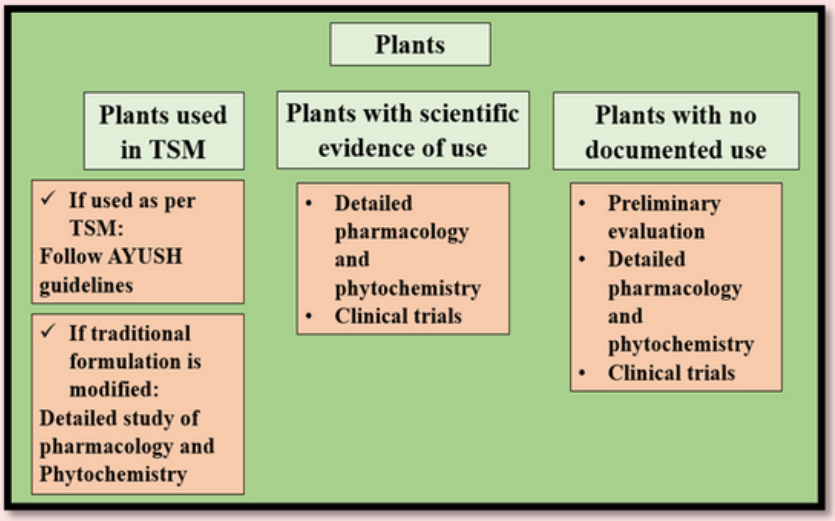


Figure 7. Pharmacological evaluation of plants

The general biological studies involve the following:

- Preliminary evaluation - selection of suitable in-vitro/ ex-vivo / in-vivo experimental model to evaluate the effect of the extracts and establish efficacy.
- Detailed pharmacological study to confirm the activity, study the mechanism of action and dose determination.
- Toxicity studies (as per OECD guidelines) - To determine the acute toxicity, sub chronic toxicity, and chronic toxicity

Then suitable formulations (according to allopathic, traditional or herbal medicine specifications) are made and commercialized.

3. Future directions

The journey seems easily doable but each step faces a number of challenges. Figure 8 highlights major constraints during the development of a phytopharmaceutical product.

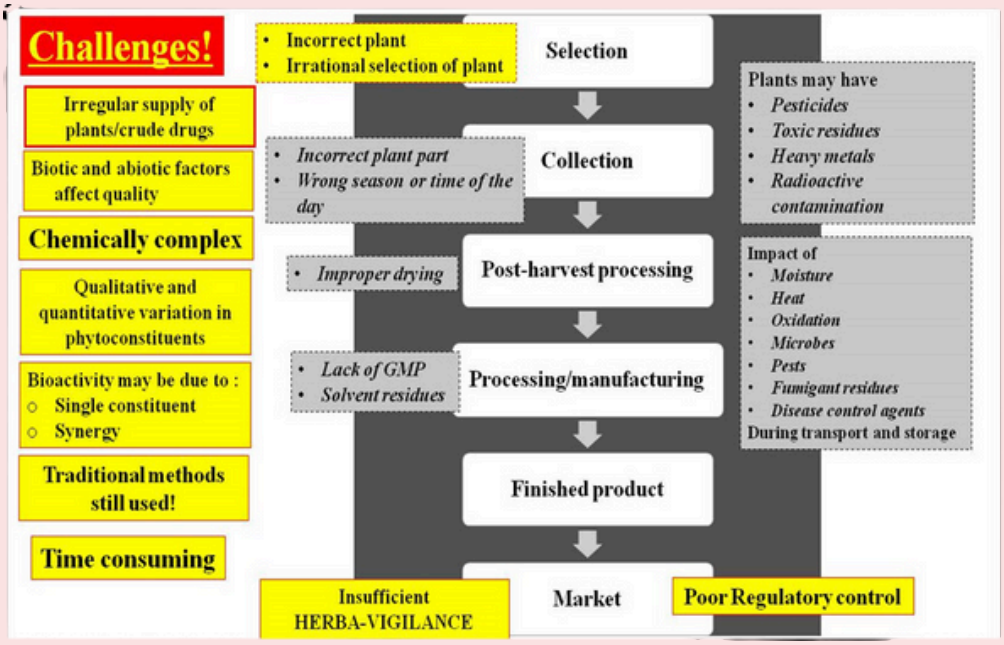


Figure 8. Challenges during the development of a phytopharmaceutical product

To overcome these challenges, figure 9 emphasises the type of testing that is essential for the raw materials (i.e. crude drugs), validation of the methods used for processing the plants and the tests that are required for evaluation of finished products (i.e. phytopharmaceutical products) (4,6).

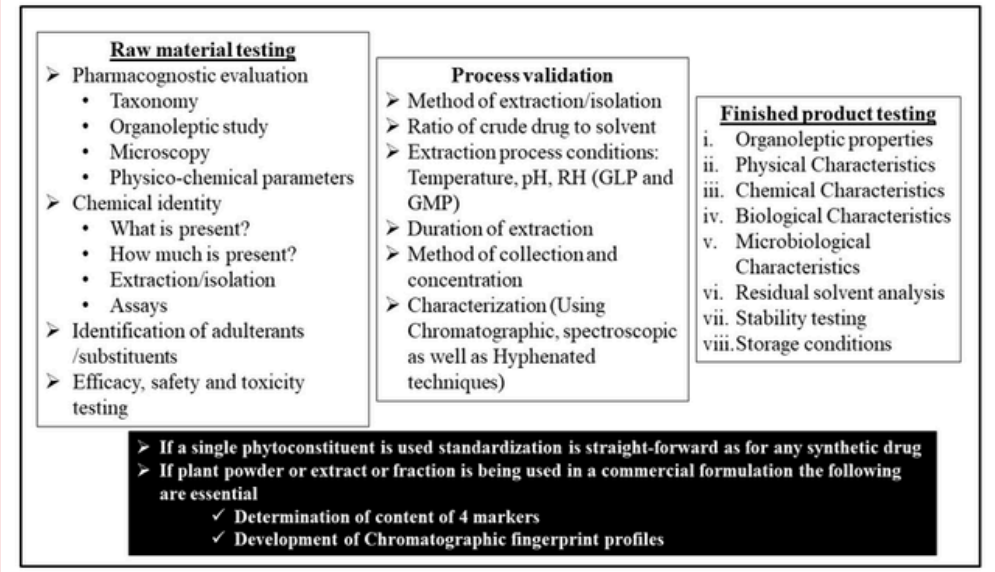
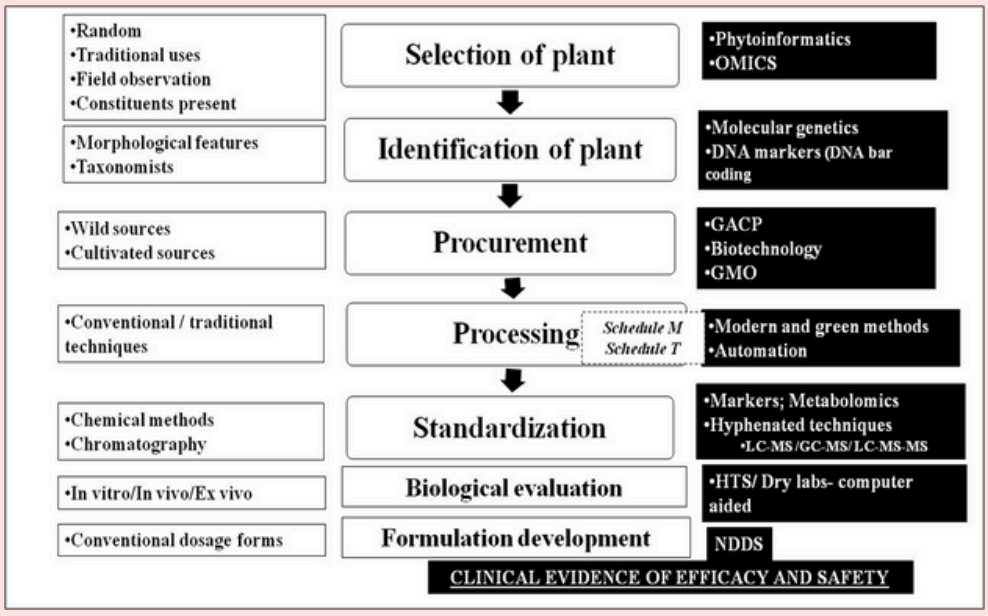


Figure 9. Testing for the development of a phytopharmaceutical product

The major objectives are to ensure a regular supply of good quality raw material (crude drugs) and to develop methods that are more specific and sensitive, faster, automated, reproducible, and cost effective.

Thus there is need to update and upgrade the steps involved. Figure 10 summarizes on what is being done and what should be included to assure that phytopharmaceutical products are of reproducible chemical purity and have reliable effectiveness and safety.



(GACP- Good agricultural and collection practices; GMO- genetically modified organisms; HTS- High throughput screening; NDDS- new drug delivery systems)

Figure 10. Current and newer methods for developing phytopharmaceutical products from plants

4. Conclusion

The key takeaways while working with plants are focus on sustainable use of plants and conservation of the environment. Along with development of commercial products with newer and faster techniques to generate detailed phytochemical profile and evidence of efficacy and safety thus leading to rational phytopharmaceutical product development.

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