CURRENT SCENARIO IN DISCOVERY AND DEVELOPMENT OF PHYTOMEDICINES

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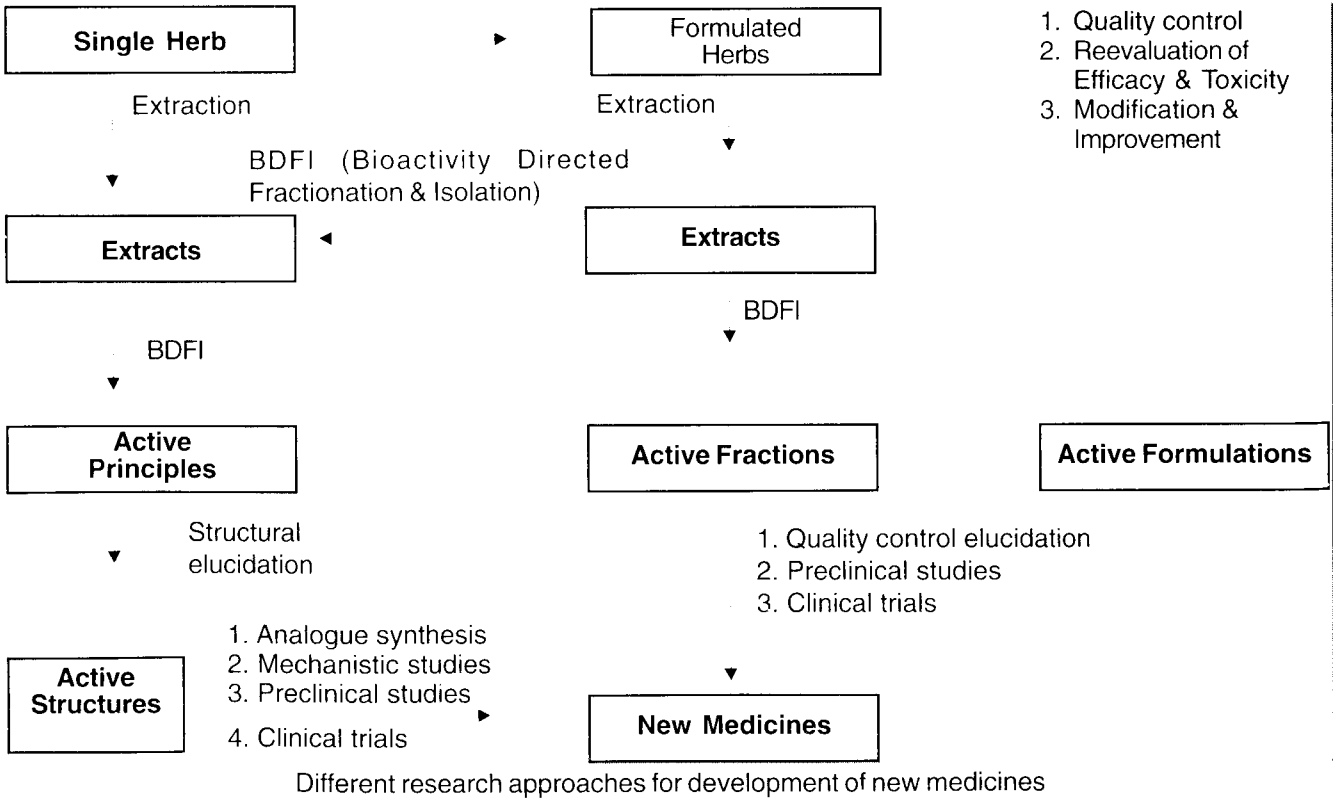
Introduction

Herbal medicines have been used since ancient times for the prevention and treatment of wide range of diseases. In spite of the great advances observed in allopathic medicine in recent decades, phytomedicines still make an important contribution to health care and quality of life. Problems with drug resistance, side effects of modern drugs and emergence of new diseases where no medicines are available, have stimulated renewed interest in plants as a remarkable source of new medicines. It is estimated that about 25% of all modern medicines are directly or indirectly derived from higher plants[1]. In some particular cases, such as antitumor and antimicrobial drugs, about 60% of the medicines currently available in the market and most of those in the late stages of clinical trials are derived from natural sources, mainly from higher plants.

It is considered that because of the structural and biological diversity, plants offer wide range of novel natural compounds, often with exciting activities and biological properties. These compounds are unique and are renewable resources for discovering potential new phytomedicines. However, as of now only 6% of the world's approximate 250,000 flowering plants have been analyzed for their possible medicinal use and rest of the plants still remain as an important source of future phytomedicines.



Different research approaches for development of new medicines

Evidence-based evaluation of phytomedicines

In olden days, plants were used either as such or as crude extracts. The irony is that though we know that a specific plant has been used for generations, we are not in position to accept their science and use them as a lead to develop phytomedicines. The current direction in medicine is practice based on evidence. While traditional knowledge and lack of good science might have been accepted previously, treatment recommendations and decisions increasingly are expected to be determined by using evidence-based guidelines. The historical acceptance of alternative medicine, or of any element of medicine, is not a sufficient standard in today's society. The revolution in biology over the past two decades has resulted in radical changes, by creating novel scientific ways for discovery and development of new phytomedicines and creating scientific evidence for the use of phytomedicines. The World health organization also has recognized the importance of traditional medicine and has been active in creating strategies, guidelines and standards for botanical medicines[2]. Global definitions of botanical products are being developed with international cooperation and a new perspective of standardization, safety and efficacy of botanical medicines are evolving.

Current approach in herbal medicine development

Currently, one of the important strategies adopted in the search for new herbal medicine consists of systematic screening of single medicinal plants, active fractions or polyherbal preparations for their biological activity. The recent approaches on phytomedicine development are shown in Fig.1 [3].

In addition, high quality, batch-to-batch consistency, and efficacy/safety are guaranteed using stringent quality control measures using various analytical and biological scientific techniques and by adopting Good Agricultural Practice (GAP), Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Clinical Practice (GCP), at each step in the development of standardized new medicines (single or multi-component) from herbal sources.

Stages in herbal medicine development

Herbal medicine development involves various steps such as formulating an appropriate strategy, gathering data on raw materials, collecting plants, obtaining extracts, high throughput screening of the extracts in appropriate assays, identification of active extracts, bioactivity directed fractionation, isolation of the active constituents and structural elucidation, phytochemical standardization, conducting preclinical tests and performing clinical trials, submitting new product application and beginning commercial production.

Selection of plants

Medicinal plants possessing the desired activities are selected based on the reports available in standard ayurvedic literatures and are validated through scientific studies.

Extraction

Extraction is a critical aspect of herbal medicine production, especially due to the low yield of extracts. Extraction methods are usually based on traditional methods such as high pressure water extraction for herbs which are traditionally boiled as decoctions and also by using different type of solvents based on their polarity. New innovative methods such as Supercritical Fluid Extraction (SFE) is being developed to produce herbal products of higher yield, lower operating costs, and to hasten production time.

Bioassay and High throughput screening

Today's high throughput screening techniques enable us to screen thousands of plant extracts and crude drug powders via several test models in a relatively short period of time, followed by the isolation and structure elucidation of all pharmacologically active components, even if they are present in a plant in minor quantities.

More recently, screening of plant extracts has been based on biochemical assays and receptor-ligand binding assays. With the increasing availability of human receptors from molecular cloning, extracts and compounds can be tested for binding directly to the presumed therapeutic target proteins. Though already known for many years in pharmacology and frequently used in industrial drug discovery programs, in studies of natural products the systematical use of these methods for screening purposes has only started recently. Several general screening bioassays including isolated subcellular systems (macrophage associated carboxypeptidases such as trypsin and kallikrein, enzymes of arachidonic acid pathway such as cyclooxygenase, 5-lipoxygenase and thromboxane-synthetase etc), isolated cellular systems (phagocytosis assay, the chemotaxis assay, various cell cultures etc) and isolated organs of vertebrates (tracheal spiral from sensitized guinea pig, segments of gastrointestinal tract or spirally cut strips of vascular tissue etc) are generally used for screening biological activity of plant extracts[4].

These bioassays operate on a molecular level (e.g., gene and receptor domains, signal transduction level) and provide a much better understanding to determine a hitherto unknown mechanism of action of a given plant extract or crude drug powder at a molecular

level, as well as facilitate the discovery of new indications. The synergistic effects of components in extract preparations can also be elucidated using molecular-biological methods.

Isolation of Active principles

The isolation and structural elucidation of all major constituents of the herbal medicine that might be responsible for its overall pharmacological activity and efficacy is an important aspect in modern herbal drug discovery. This can be performed with or without a bioactivity guided fractionation using the modern chromatographic and spectroscopic techniques available[5]. Great progress in this area has been achieved through the application of specific and selective analytical methods, using a combination of high performance liquid chromatography (HPLC) and diode-array technique (online recorded ultraviolet [UV] spectra), or mass spectrometry (MS) and nuclear magnetic resonance (NMR) detection.

Standardization of Plant extracts

The elucidation of the major active constituents aims primarily at the standardization of an extract which is based on the true bioactive compounds of an extract. The recent advancements which has occurred in the process of purification, isolation and structural elucidation of naturally occurring substances have made it possible to establish appropriate strategies for the analysis of quality and the process of standardization of herbal preparations in order to maintain the homogeneity of the plant extract as much as possible. Because several constituents contribute to the overall pharmacological and therapeutic effects of an extract, the quantitation of one marker compound or a collection of compounds according to a pharmacopoeia or a national monograph will no longer be sufficient. In these cases, the standardization method is aimed at the quantitation of two or three major bioactive components, as evaluated by pharmacological investigations[6]. The single extracts are standardized or fingerprinted before mixing the individual extracts, or a 3D HPLC fingerprint analysis of the multicomponent extract mixture is performed.

Determination of Effective dose

The efficacy and safety of the herbal medicine is established through *in vivo* studies. The main objective of *in vivo* study is to understand and predict the effects of plant extracts on the whole organism in order to determine the effective dose and to prove that the plant extract is nontoxic and has minimum side effects. In possible situation pharmacokinetic testing is done to provide data on how the phytomedicine is absorbed, distributed, metabolised and excreted (ADME) from the body.

Stability Studies

Stability studies to evaluate the effect of plant extracts and polyherbal formulations over a period of time are performed to ensure the presence of active constituents, desired biological activity and safety.

Clinical Trials

Once the herbal medicine has proved its efficacy in animal experiments, studies on humans follow. The efficacy of phytopharmaceuticals in humans can be conclusively proven only by a controlled clinical trial. So the herbal medicines are subjected to the double-blind, randomized, placebo-controlled clinical trial in order to prove the efficacy in humans. In addition, bioavailability and pharmacokinetic studies for phytopharmaceuticals are conducted in humans to disprove the oft-expressed opinion that phytopharmaceuticals are placebos because no active constituents there-of could be detected in the body after administration. The scientific advantages, however, are obvious. Pharmacological effects can be correlated with clinical efficacy, dose regimes can be optimized, a better application form can be found, to improve absorption of the phytopreparations from the gut, metabolization and elimination pathways can be elucidated, and possible interactions between herbal constituents and other co-medicated drugs can be detected.

At present more than 400 single and double-blind placebo-controlled clinical trials that meet all international requirements of performance and efficacy have been reported. About 80 percent of the existing studies were done with the 14 herbs such as Ginkgo, Echinacea etc and the remaining with polyherbal preparations[7].

Conclusion

Medicinal plants have provided most of the drugs in use. Despite the achievements in synthetic chemistry and the advancements in rational drug design, plant products continue to possess huge potential in providing mono and polyherbal medicinal preparations and as source for the development of synthetic analogues. Hence in the new era of drug discovery and development based on medicinal plants, there can be two pathways, one the traditional method of drug discovery based on active principles, hit and trial method and the other based on the ethnomedical approach, having a sound knowledge of the Ayurvedic principles. An appropriate strategy with judicious application of traditional knowledge and modern science of drug discovery and development can enhance the speed and lessen the time and money required for development of effective and safe phytomedicines. ❑