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### Present status, standardization and safety issues with herbal drugs

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#### ABSTRACT



Traditional use of medicine is a vital component of the health care system throughout the whole world. The term herbal medicine refers to the use of herbal plants for preventing and treating various ailments. It includes popular traditional herbs of every nation to the usage of analyzed and standardized herbal extracts. However treatment strategies involving the use of these agents have shown promising outcomes with the efficacy of a good number of herbal products clearly elucidated. Although many of these agents remain unchecked and their use are either poorly regulated or not even regulated at all. Herbal-based therapeutic agents should undergo a powerful assessment of their pharmacological activities and safety concerns because of large and growing use of herbal derived substances globally. Even throughout the world, research on herbal medicine safety is still not enough so that their efficacy and adverse effects can be documented well. To overcome this, studies on the toxicity and the interactions between herb and drug used in herbal medicines, which is of utmost importance, should be studied. For monitoring clinical safety of drugs, spontaneous reporting system or active Pharmacovigilance is useful in recognition of therapeutically relevant safety issues and recording them with the concerned authorities. In this paper, a small step has been taken to summarize the information described in scientific research conducted about Present status, Standardization and safety concerns of herbal drugs.

**Keywords:** Adverse effect; clinical trials; Herbal drugs; Pharmacovigilance.

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#### INTRODUCTION

Herbal drugs have been used to treat various types of health ailments from past several hundreds of years. Even in the modern times, people are getting more attracted towards using herbal drugs to cure various

ailments. Several clinically efficacious drugs that currently play a major part in treating and preventing various human diseases have been developed from natural sources such as by microbial fermentations or from plant extracts. Reserpine, atropine, quinine, penicillin G, morphine, digoxin, cyclosporine etc. are some of the well-known natural products originated drugs, which act as milestones in the history of modern medicinal therapy. It has been observed that about 50% of the best selling pharmaceuticals were obtained from natural sources or their derivatives. In addition, up to 60% of different drugs such as anti-tumor and anti-infective drugs that are commercially available or in later stages of clinical trials today are of natural product origin. Several studies have estimated that more than 70% of the world population still relies on plants as the major source of medicines in their primary health care. However the irony is that, only a small fraction of the estimated 400,000-500,000 plant species globally that have been phytochemically investigated, and in addition, only a few constituents have undergone biochemical, biological or pharmacological screening for their validation of their activity.<sup>[1]</sup> The World Health Organization has shown a keen interest in documenting and recording the use of medicinal plants by indigenous people from all around the world. <sup>[2]</sup> Documenting and recording of traditional knowledge about the usage of

medicinal plants is vital due to several reasons for e.g. indigenous culture heritage is preserved from being lost for the use of both present and future generations. [3] Using plants for healing purposes back date to human history and forms the basis of much modern medical therapy. Several pharmaceutical agents in current clinical practice, available to doctors have a long history of use as herbal remedies, viz. opium, Aspirin, Digitalis and Quinine etc. [4] This is usually because of the general thinking that herbal drugs are devoid of any side effects besides also being locally available. [5,6] Moreover, pharmaceuticals are prohibitively expensive for most of the world's population, half of which lives on less than \$2 US per day. [7] The search for, plants of medicinal value and dietary supplements derived from plants and leads that could be developed for treatments of various diseases have picked pace in recent years. [8] Among the 120 active compounds currently obtained from the higher plants and widely used in modern medicine today, 80% show a positive relation between their modern therapeutic use and the traditional use of the plants from which they were obtained. [9] In last decade, a tremendous rise in acceptance and public interest in natural therapies both in developing as well as developed countries has been observed. It is estimated that more than 70% of the world's population living in the developing world use herbal medicinal products as a primary source of healthcare and traditional medical practice. The use of herbal medicines is viewed a central part of the culture in these communities. [10-13]

### Present status of herbal drugs

Herbal agents are naturally occurring products. Their chemical constitution varies according to several factors. It differs from decoctions to the use of herbal extracts following Western methodologies of mainstream medicine. Herbal medicines have a very long history. It is summation of the practices dependent on the speculations, convictions and encounters of various societies and times, frequently mystifying, utilized in the support of wellbeing of health, as like in the anticipation, finding, improvement and treatment of different diseases. In every nation, indigenous medicines find base in magical or religious beliefs, or popular experience and the World Health Organization is actively engaged to establish definitive guidelines for methodology of clinical research and the appraisal of effectiveness of traditional medicine in practice. [14] The wide spread utilization of herbal medications isn't constrained to developing nations, as it has been evaluated that over half of every single clinical specialist in France and German normally recommend natural medication routinely. With this the quantity of patients looking for natural methodologies for treatment is likewise developing colossally. With the US Food and Drug Administration (FDA) relaxing guidelines for the sale of herbal supplements, the market is booming with herbal products and these are readily available in the market. [8] Since past

several years, an unusual thing has happened to traditional medicine that instead of being neglected with the advent of medical science and pharmaceutical chemistry, it has made a promising come back. [13] Various compounds cannot yet be synthesized economically and are still obtained from natural sources. Natural compounds can be parent compounds and may help the scientists in the designing and planning of new drugs, biomimetic synthesis, development and the discovery of new medicinal properties not yet attributed to any known compounds. In addition, several agents viz. muscarine, physostigmine, cannabinoids, yohimbine, forskolin, colchicine and phorbol esters etc., all obtained from plants, and are important tools being used in pharmacological, physiological and biochemical studies. The usage of herbal medicines continues to rise rapidly throughout the globe with many people now using these agents for treatment and mitigation of various health challenges in several national healthcare settings. [15]

### Natural herbs as source of pharmacological tools

Natural herbs have served the mankind and still will act as an important source of new drugs. Another important role of natural products in medical research is their utility as pharmacological tools for the identification and investigation of the physiological functions of receptors and enzymes, which serve or possibly will serve as drug targets for many targets. For instance, physostigmine, nicotine and curare have made a significant contribution to the research of the nicotinic receptors. In the field of intracellular signal transduction, for example, has been developed, in large part, through the study of cyclosporine, FK506 and rapamycin. The phorbol esters from the Euphorbiaceae or Thymelaeaceae families have played a huge important role in the investigation of the protein kinase C and have contributed to the identification of a further receptor RX kinase (RX is the C-20 homovanillate of 9, 13, 14-ortho-phenylacetyl-resiniferol). These enzymes are of great importance in the understanding of several disease conditions such as inflammatory response, cancer, cell proliferation, viral expression etc. [1]

### Safety issues with herbal drugs

Herbal drugs have been a popular form of healthcare therapy; even though several differences exist between herbal and conventional pharmacological treatments. However herbal drugs needs to be checked for efficacy using conventional trial methodology and several specific herbal extracts has been demonstrated to be efficacious for specific conditions. However the people are often misinformed to believe that all natural treatments are inherently safe, although herbal medicines do carry risks, so research in this area must be intensified and carried forward. The necessary question that has not been often answered satisfactorily deals with the AME i.e. absorption/metabolism/efficacy of herbs and their extracts which is actually an unsolved mystery in judging their

many alleged health effects. [14] Traditional herbal products are heterogeneous in nature. They pose a certain number of challenges to quality control, quality assurance and the regulatory process. Mostly the herbal products in the commercial use have not been subjected to any drug approval process to validate their safety and effectiveness. Some of them contain mercury, lead arsenic and corticosteroids, poisonous organic substances and aflatoxin in harmful amounts. [16] As the widespread use of herbal medicinal products continues to increase day by day and many new agents are being introduced into the market ever now and then, public health issues, and issues regarding their safety are also increasing day by day. The information about their potential adverse effects is also very limited as most of their adverse effects have not reported and identification of the safest and most effective therapies as well as the promotion of their rational use could become more difficult. It is also a well known fact that the safety of most herbal products is further compromised by lack of suitable quality controls, inadequate labeling, and the absence of appropriate patient information and standardization of doses. [17, 18] The general impression is that the herbal agents are very safe without any adverse effects, which is not only untrue, but also misleading as they usually don't follow a proper regulatory process. Herbs are capable of causing undesirable and unintended adverse reactions, many of which are capable of leading to serious health hazards. Numerous cases of poisoning have been seen and reported in the literature. [19-21] Sometimes patients use herbal and conventional allopathic medicines concomitantly resulting in serious drug interactions. There are reports of serious adverse events after administration of herbal products. In most cases, the herbs are usually self-prescribed and usually bought over the counter or brought from a source other than a registered practitioner. [22] As the plant materials are in use in both developed and developing countries as home remedies, over-the-counter drug, products and raw materials for the pharmaceutical industry, and represent a substantial proportion of the global drug market. It is therefore imperative to establish internationally recognized guidelines for assessment of their quality, assuring their quality and regulatory process. [23, 24] All herbal medicines are composed of combination of more than one active ingredient and the mixture is usually composed of several ingredients. Mixture of active ingredients will lead to an increase in the chances of interactions between herbal medicines and conventional drugs and could lead to fatal issues. Moreover, users of medicinal drugs are primarily suffering from chronic illnesses for which they are likely to take prescribed drugs concomitantly i.e. polypharmacy. This, in turn, further adds up the potential of herb-drug interaction. Several studies have explained this viz. In a study, it was observed that the prevalence of concomitant herbal medicinal products and antipsychotic treatment was 36.4% (34.2%–38.6%). Herbal medicine drug regimens containing Fructus

Schisandrae Chinensis, Radix Rehmanniae, Akebia Caulis, Radix Bupleuri, Fructus Gardenia, and Semen Plantaginis in synergistic use with clozapine, quetiapine, and olanzapine were associated with nearly 60% of the risk of adverse events. [24, 25] With the ever increasing consumption of herbal products and medicines, it is high time they are included in pharmacovigilance systems and all the adverse events are documented and properly recorded. In terms of population exposure alone, it is important to identify the risks and benefits associated with the use of herbal medicines, and in this context, the safety of these products has become an issue of great public health importance. [26]

### Standardization of herbal drugs

In herbal medicine, the drugs are usually prepared as water decoction. Fresh, dried plant parts, juice or crude powder forms are rarely used. Thus medicinal plant parts should be original without any harmful contaminants such as chemicals, heavy metals, microbial or radioactive contamination, pesticides etc. The plant with medicinal property is primarily subjected to a single solvent extraction once or repeatedly, or water decoction or as described in several studies. The extract should then be tested and screened for proposed biological activity in an experimental animal model. The active ingredient should be standardized and analyzed on the basis of active principle or major compound along with full drug profile (fingerprints). The next necessary step is stabilization of the bioactive extract with a minimum shelf-life of over a year. The stabilized bioactive extract should undergo regulatory or limited safety studies in experimental animals. Finding probable mechanism of action will elaborate the therapeutic profile of the active constituent. The safe and stable herbal extract may be marketed in a proper formulation if its therapeutic use is well documented in indigenous systems of medicine, as also viewed by World Health Organisation and also showing desired results in animal models and has been successfully fulfilling all the qualities of a good drug. A proper clinical trial helps to contribute in establishing its therapeutic potential and promotes its clinical use and help in supporting its use in clinical practice. [8]

### CONCLUSION

Traditional herbs have been employed for treatment and prevention of various diseases in throughout the world from last several hundreds of years. In nature, there is enormous variety of herbs, having medicinal properties and used to prepare the herbal medicines. Herbal medicine is an effective treatment strategy that uses different plant parts or their extracts. In the modern era, herbal medicine or drugs from natural sources has become a promising and popular type of healthcare strategy; although there are several differences between traditional and conventional pharmacological therapies. In addition herbal medicines need to be verified for efficacy using clinical trial

methods and should follow proper quality control, quality assurance and regulatory processes. Lastly, safety evaluation system made up of rational clinical practice and risk monitoring should be established to improve the safety use of herbal medicine in maintaining human health and further elucidating their profile.

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