Chapter-1
Introduction

1. INTRODUCTION

1.1 Traditional medicine

Traditional medicine (also known as indigenous or folk medicine) comprises of medicinal knowledge systems that are developed over generations within various societies before the era of modern medicine (WHO, 2008). It 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 illnesses. The terms *complementary/alternative/non-conventional* medicine are used interchangeably with traditional medicine in some countries.

WHO defines Traditional Medicine (TM) as "health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being" (WHO, 2000).

The use of plants, parts of plants and isolated phytochemicals for the prevention and treatment of various health ailments has been in practice from time immemorial. Basically India has a tradition of codified healthcare systems: Ayurveda, Unani and Siddha, which function mainly through (1) folk stream and (2) classical stream. The former, is based on oral traditions, practiced by villagers and the tribal communities while the later comprises the codified systems supported by theoretical knowledge, experimental and philosophical explanations provided by many learned physicians and surgeons of earlier time like *Charak, Sushruta, Galen, Rhazes, Avicenna*, and others. The preventive, corrective and curative approach of health is the basic strength of these systems of medicine. The ancient civilizations developed their systems of medicine (Ayurveda, Unani and Siddha) independent of each other but all of them were predominantly plant based and comprise over 8000 medicinal and aromatic plants species (http://indiahomeclub.com). This is the highest proportion of medicinal plants known for their medical purposes in any country of the world for the existing flora of that respective country (Chandra et al., 2006; Edwin et al., 2007). Demand for medicinal plant is increasing in both developed and developing countries due to growing recognition of natural products, being non-narcotic, having no side-effects,

easy availability at desirable price and sometime the only source of health care available to the poor.

In fact, according to the World Health Organisation, approximately 25% of modern drugs used in the United States have been derived from plants.

- ✓ Among the 120 active compounds currently isolated from the higher plants and widely used in modern medicine today, 80 percent show a positive correlation between their modern therapeutic use and the traditional use of the plants from which they are derived.
- ✓ More than two thirds of the world's plant species - at least 35,000 of which are estimated to have medicinal value - come from the developing countries.
- ✓ At least 7,000 medical compounds in the modern pharmacopoeia are derived from plants (Fabricant and Farnsworth, 2001; European Union, 2000-2005).

We can say, traditional use of medicines is recognized as a way to learn about potential future medicines.

Even though these traditional claims on medicinal plants are direct clinical clues, very often they are unscientifically exploited and/or improperly used. These medicinal plants deserve detailed studies in the light of modern science and also need effective assessment in terms of their chemical composition and bioactivity profile.

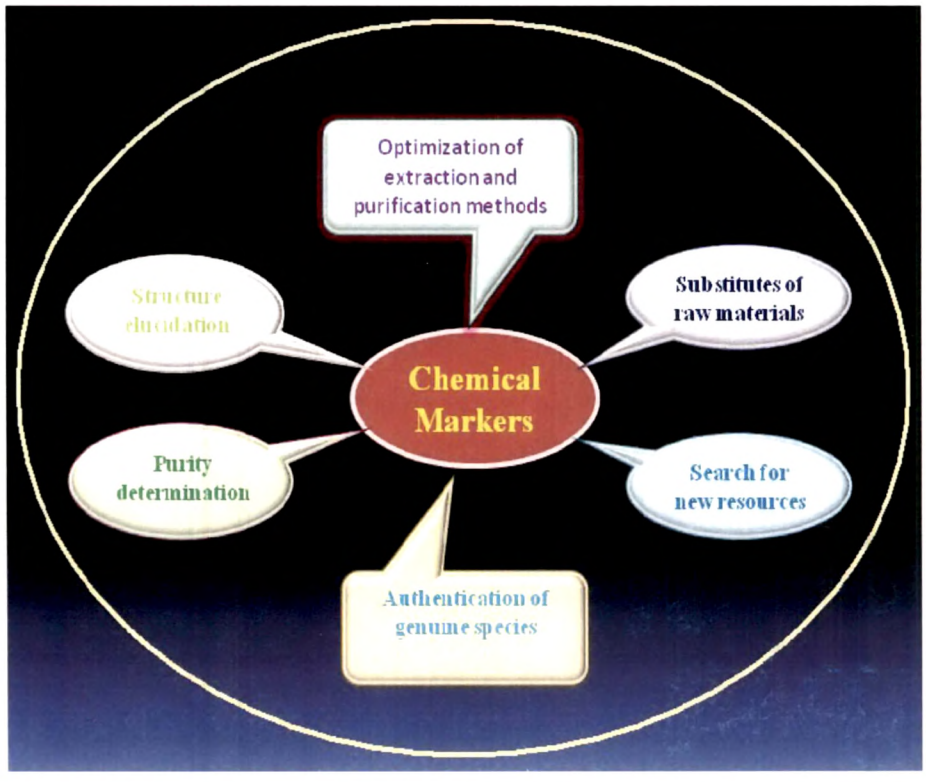
1.2 Chemical Markers/ Biological Markers

All plants produce chemical compounds as part of their normal metabolic activities. These are arbitrarily divided into primary metabolites, such as sugars and fats, found in all plants, and secondary metabolites, compounds not essential for basic function found in a smaller range of plants, some useful ones found only in a particular genus or species. Among these secondary metabolites around 12,000 have been isolated which is estimated to be less than 10% of the total. Many plants also synthesize substances that are useful to the maintenance of health in humans and other animals. These include aromatic substances, most of which are phenols or their oxygen-substituted derivatives such as tannins (2004; Lai and Roy, 2004).

According to European Medicines Agency (EMEA) chemical markers are defined as chemically defined constituents or groups of constituents of a herbal medicinal product which are of interest for quality control purposes regardless whether they possess any therapeutic activity (http://www.emea.europa.eu). Ideally, chemical markers should be unique components that contribute to the therapeutic effects of an herbal medicine. As only a small number of chemical compounds were shown to have clear pharmacological actions, other chemical components are also used as markers. The quantity of a chemical marker can be an indicator of the quality of an herbal medicine.

Moreover, the study of chemical markers is applicable to many research areas, including authentication of genuine species, search for new resources or substitutes of raw materials, optimization of extraction and purification methods, structure elucidation and purity determination. Systematic investigations using chemical markers may lead to discoveries and development of new drugs.

Fig. 1.1 Application of chemical markers in research area



Quality control of herbal medicines aims to ensure its quality, safety and efficacy. Chemical markers are pivotal in the current practice of quality control. Chemical markers should be used at various stages of the development and manufacturing of an herbal medicine, such as authentication and differentiation of species, collecting and harvesting, quality evaluation, stability assessment, diagnosis of intoxication and discovery of lead compounds. Lack of chemical markers remains a major problem for the quality control of herbal medicines. In many cases, we do not have sufficient chemical and pharmacological data of chemical markers. Furthermore, there are many technical challenges in the production of chemical markers. For example, temperature, light and solvents often cause degradation and/or transformation of purified components; isomers and conformations may also cause confusions of chemical markers.

1.3 Liver disorders and herbal medicines

Mammalian liver is a key organ associated with regulating physiochemical functions of the body including synthesis, secretion and metabolism of xenobiotics. Therefore, hepatic injury in form of liver cells toxicity causes impairment of liver function and associated physiological complications (Mroueh et al., 2004). Infectious agents and hepatotoxic chemicals are the main causative agents inducing impairment of liver function (Navarro and Senior, 2006). Drugs having beneficial effect on the liver are known as hepatoprotective drugs.

A large number of population suffer, due to various reasons, from hepatic diseases and also inflammatory condtions of known and unknown origin. Thus identification and isolation antihepatotoxic drugs is being the major thrust area and has drawn attention of majority of workers in the field of natural product research. Currently available hepatoprotective drugs are effective but the patients run a risk of developing side effects. Hence, ethnomedicines of herbal origin and phytoconstituents extracted from medicinal plants with proven hepatoprotective potential could be an effective alternative in the treatment of liver diseases (Stickel and Schuppan, 2007). Many mono and poly-herbal preparations have been used in various liver disorders. According to one estimate, more than 700 mono and poly-herbal preparations in the

form of decoction, tincture, tablets and capsules from more than 100 plants are in clinical use. (Singh Amrit Pal; Stickel and Schuppan, 2007). Infact in Ayurveda also, there are a wide variety of herbal treatments suggested for prevention of liver disorders (Chatterjee, 2000). Some important and popular medicinal plants used as hepatoprotectives are described in Table 1.1

Table 1.1 Some important medicinal plants used in liver disorders

S. No.	Name of plant	Vernacular name	Chemical Constituents	Traditional system of medicine	References
1	Glychyrrhiza glabra Linn	Liquorice or *Mulethi*	Glycyrrhizin	Ayurveda	Stickel and Schuppan, 2007
2	Phyllanthus amarus		Phyllantins, hypophyllantins	Ayurveda	Calixto et al., 1998
3	*Berberis aristata* DC	Indian Barberry	Berberine	Western herbal medicine	Singh Amrit Pal, 2007
4	*Tecomalla undulata* G.Don	*Ragat rohida*	-	Ayurveda	Singh Amrit Pal, 2007
5	*Picrorhiza kurroa*	Royle or *Kutki*	Kutkin	Ayurveda	Saraswat et al., 1997
6	*Eclipta alba* (L.)	*Bhringraja*	Wedelolactone	Ayurveda	Saxena et al., 1993
7	*Curcuma longa* Linn.	Turmeric or *Haldi*	Curcumin	Ayurveda	Deshpande et al., 1998
8	*Andrographis paniculata* Nees	*Bhunimba* or *Kalmegha*	Andrograph-olide	Ayurveda	Trivedi and Rawal, 2001

Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver diseases. The limiting factors that contribute to this eventuality are (i) lack of standardization of the herbal drugs; (ii) lack of identification of active ingredient(s)/principles(s); (iii) lack of toxicological evaluation (Radha *et al.,* 2005).

1.4 Selection of plant materials

Medicinal plants were selected on the basis of their reported claims as hepatoprotective in traditional medicines and the scope they offer for further studies:

1. *Feronia limonia* Linn. Family-Rutaceae (Syn. *Limonia acidissima, Feronia elephantum (corr)*
2. *Tecomella undulata* Seem. Family- Bignoniaceae (Syn. *Bignonia undulata*)

1.5 Standardization of herbal drugs

The increasing demand for herbal medicines inevitably led to the issue of obtaining and maintaining their quality. As a result there has been tremendous quality consciousness for the herbs in many countries. National and International pharmacopoeias too have provided monographs stating quality parameters and standards for many herbs. World Health organization (WHO) provided various guidelines on the quality control methods for medicinal plant materials. These guidelines take into consideration various pharmacognostic parameters, proximate analysis, chemical and biological evaluation, to ensure the quality avoiding batch to batch variations starting from the collection of plant material upto the prepared formulations.

Main attributes of standardization and quality assurance are authenticity, purity and assay of material. Authenticity as the name suggests relates to proving that the material is true i.e., it corresponds to right identity (morphology, microscopy and chemical analysis). Purity pertains to evaluating that there is no adultrants present in the plant material (qualitative, quantitative microscopy, ash value determination). Assay includes chemical and biological profiling through which biological & chemical effects can be established. In biological assay, drug activity is assessed through *in vitro* and *in vivo* pharmacological models.

1.5.1 Standardization of botanicals by HPTLC

WHO in a number of resolutions has emphasized on the need to ensure the quality control of herbs and herbal formulations by using modern techniques. In a herbal extract (total) there are numerous fractions present which add to the efficacy of product. The total extract can be characterized by its fingerprinting. Goverment of India has adopted the fingerprinting approach for botanicals because it supports the traditional concept and is easy to practice at different levels of sophistication. A chromatographic method that does quantification of a specified fraction(s) as well as

fingerprinting is considered as ideal. Chromatographic techniques which are used for separating mixtures into individual fractions are ideal for creating a fingerprint. One such technique is High Performance Thin Layer Chromatography (HPTLC) technique which is well suited to obtain a detailed fingerprint of herbal extract or product. It comprises of UV scanning, fluorescence, UV spectra and photographic image in UV light (254 and 366 nm) and occasionally in visible light after derivatization. HPTLC fingerprinting is obtained at low cost and high speed and thus meets the need for a modern quality control method (Charegaonkar, 2005).

Standardization can be done in two ways:

1) Standardization of herbs using biomarker compounds
2) Standardization of herbs using chemical marker compounds

✓ **Standardization of herbs using biomarker compounds**

Every herb has a range of chemical constituents, which are produced as a result of metabolic activities in the plant. If these compounds either alone or in combination are mainly responsible for the pharmacological activities or therapeutic action in the human body, they are termed as biomarker compounds. Eg. Curcumin or curcuminoids in turmeric. When these compounds are used for testing the autneticity of drug it is known as Standardization of herbs using biomarker compounds. It would be more practical to test for the presence of these compounds.

✓ **Standardization of herbs using chemical marker compounds**

On the other hand where the chemical composition of the herbs has been worked out but it is not clearly established whether these chemical entities are responsible for some particular action, any compound which is predominantly present in the herbs can be utilized as marker for the purpose of standardization. Although the activity of these compounds are not linked with any therapeutic purposes but their presence has been well established in such plants and hence they can be used for standardization purpose (Dobriyal and Narayana, 1998).

Including these techniques High performance liquid chromatography (HPLC) techniques can also be used for standardization purpose.