# CHAPTER-1

## Chapter - 1. INTRODUCTION

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CHAPTER - 1

1. INTRODUCTION

Herbal medicine has a long history in the treatment of several kinds of diseases\(^1\). Their use for the treatment of diseases have been practised by man for many years and is still being widely practised even today\(^2\). For many years, people have developed a store of empirical information concerning the therapeutic values of local plants before orthodox medical practice appeared. With the experiences of trial, error, and success, these herbalists and their apprentices have accumulated a large body of knowledge about medicinal plants. The first generation of plant drugs were usually simple botanicals employed in more or less their raw form. Many effective medicines used in their natural state were selected as therapeutic agents based on empirical study of their application by traditional societies from different parts of the world\(^3\).

Through the periods of the industrial revolution, next generation of plant based active medicaments emerged based on scientific processing of the plant extracts to isolate their active principles. Medicinal plants play an important role in combating serious diseases in the world; for the therapeutic approach to several pathologies. Interest in medicinal plants has been overwhelming in the recent times especially as an important source of medication. Presently, the global market for medicinal plants has been estimated to be around US $62 billion and the demand is growing rapidly\(^4\). It is globally recognized that medicinal
plants play a significant role in providing health benefits to human beings. The World Health Organization (2000) has estimated that 80 % of the inhabitants of the world rely mainly on traditional medicines for their primary health care needs, and it may be presumed that a major part of traditional healing involves the use of plant extracts or their active principles.

Infectious diseases account for approximately one-half of all deaths in tropical countries. Medicinal plants have been traditionally used for different kinds of ailments for all pathological conditions. Plants are rich in a wide range of secondary metabolites like alkaloids, tannins, terpenoids and flavonoids that were found to have antimicrobial properties. Historically, plants have provided a good source of anti-infective agents. Emetine, the isoquinoline alkaloid obtained from the *cephaelis ipecacuanha*, and its species, has been used for many years as an amoebicidal drug for the treatment of abscesses due to the spread of *Escherichia histolytica* infections. Quinine, an alkaloid from the bark of the Cinchona tree, is also very important drug of plant origin with a long history of usage against malaria. The higher plants have made important contributions in areas such as cancer therapy etc. Scientists from divergent fields are investigating plants with an intention to discover valuable phytochemicals. Research laboratories all over the world have found literally thousands of phytochemicals which have inhibitory effects on all types of microorganisms *in vitro*.
With the brisk progress in the field of medicine and its allied sciences the synthesis of many chemicals and their introduction into therapeutics as drugs certainly revolutionized the treatment of diseases. Today we have a large number of synthetic drugs that are efficient against many diseases.

When there is a surfeit of such established drugs, it may look a little bit odd if one tries to go back to indigenous drugs and bring out new therapies. The scientists of synthetic medicines will be the strongest critics of such a progress. They produce a large array of adverse reactions and have been the cause of a number of diseases. Alternative attention should be the cost factor. Many of the synthetic drugs are expensive for the common man. It is natural that under these circumstances, to understand the intentions behind a person’s interest in the field of natural products and the drugs obtained from the rich flora and fauna of this ancient land. Nature has an enormous diversity of chemical compounds namely secondary metabolites that are considered as waste products but maintains strong relationship between organism and environment\(^7,8\).

The necessary features required for the biological relevance is fulfilled by natural products as they have evolved to interact with multiple proteins and can be regarded as embodying privileged structures that can bind to various proteinaceous receptors. These are synthesized by more than one protein, hence they generally display
multiple biological activities mediated by interaction with different proteins.

The claims of therapeutic efficiency and lack of toxicity of many plants have been scientifically proved in the past few decades. However, there is notable number of questionable value among the reported indigenous drugs. There are large numbers of plants, which have to be examined thoroughly for useful activity or lack of it. It will be a worthy research if one tries to select the best out of them.

1.1 THE VALUE OF PLANTS USED IN ETHNO MEDICINE:

Medicinal plants provide a rich source of raw materials for primary health care in Africa and other parts of the developing world. Notable examples were quinine from Cinchona pubescens, taxol from Taxus species and reserpine from Rauwolfia serpentina. Various plant based drugs are listed in Table 1.1. The sequence for development of pharmaceuticals usually starts with the identification of lead molecule, bioassay, and then formulation of suitable dosage form. Later, this is authenticated by several phases of clinical studies designed to establish safety, efficacy and the pharmacokinetic profile of the new drug. During the last few decades, there has been a resurgence of interest in plants as source of medicines and of novel molecules for use in the elucidation of physiological/biochemical phenomena. There is the worldwide green revolution, which is revealed in the confidence that herbal remedies are safer and less damaging to the human body than
synthetic drugs. Still, initially this growth of interest in plants is the fact that many important drugs in use today were derived from plants or from starting molecules of plant origin: digitalis glycosides, the vinca alkaloids and pilocarpine are few important examples.

Laboratories around the world are engaged in the screening of plants for biological activity with therapeutic prospective. The impending of higher plants as sources for new drugs is unexplored\(^\text{11}\). Among more than 2,50,000 species of plants, a small number of about 5-10 % has been investigated chemically for the presence of biological active compounds\(^\text{12, 13}\).

**1.2 POSTULATE AND IMPETUS OF STUDY:**

Natural product research continues to provide a tremendous variety of lead structures, which are used as prototypes for the expansion of new drugs by the pharmaceutical industry. Many of the plants studied have shown very promising activity in the area of antiviral agents. Also many species of plants have been found to be active against a wide variety of micro-organisms\(^\text{13, 14}\). The plant kingdom still represents an enormous reservoir of new molecules to be discovered.

**1.3 PROSPECTIVE OF NATURAL PLANT PRODUCTS:**

Plants represent the second largest source of biodiversity. India is represented by prosperous natural biodiversity and offers a unique opportunity for drug discovery researchers. The country is blessed with Eastern Himalaya and Western Ghats, which are world’s 18 hotspots of
plant biodiversity where 70% of the species occur collectively and is 7th among the 16 Mega assorted countries\textsuperscript{15, 16}.

Nature has an enormous diversity of chemical structure, which is not waste products, but specialized secondary metabolites involved in the relationship of the organism with the natural world\textsuperscript{17, 18}.

**1.4 ADVANTAGES OF PLANT DERIVED MEDICINES:**

The plant-derived medicines have three distinctive benefits over the more conventional techniques of phytochemical research. India is represented by prosperous natural biodiversity and offers a unique opportunity for drug discovery researchers. More than 7500 plant species have been reported to be used in the Indian traditional systems including ethno medicines\textsuperscript{19, 20}.

Keeping all the above points in view, the following plants have been selected for a thorough investigation related to their pharmacognosy, phytochemical and pharmacological properties and a through literature survey has been carried out and documented in this thesis.

1. *Basella rubra* L. (Basellaceae)

2. *Phyllanthus acidus* L. (Phyllanthaceae)

**1.5 NATURAL PRODUCTS AS LEAD MOLECULES IN DRUG DISCOVERY:**

Natural products have been proven templates for the development of new drugs\textsuperscript{21}. Several methods have been utilized to acquire compounds for drug discovery including isolation from plants and other
sources like, synthetic chemistry, molecular modeling and combinatorial chemistry\textsuperscript{22-28}.

1.6 BIOASSAYS\textsuperscript{29}:

In any natural product isolation programme in which the end product is to be a drug or a lead compound, some kind of pharmacological evaluation or bioassay screening must be necessarily used to guide the isolation towards the pure bioactive compound. The biomass is to be collected, dried, and extracted using suitable solvent mixtures to get an extract, which is later screened for bioactivity. Bioassays could involve the use of \textit{in vivo} systems such as experimental trials, entire animal tryouts, \textit{ex-vivo} systems such as isolated tissues and organs and \textit{in vitro} systems such as cultured cells. Often bioassays are linked with the process of fractionation and isolation, known as bioassay-guided fractionation involving chromatographic techniques and are used to separate the extract into its discrete components. The biological activity is tested at all levels until a pure active compound is obtained. Given below is a broad classification of bioassays for phytopharmacological screening:

1.6.1 General Screening Bioassays:

These are non-selective and indicate whether or not a certain extract/compound is active. Active compounds from such assays (Biomarkers) can later be subjected to specialized assays. Hippocratic screening uses intact animals and involves the effect of plant extracts or
their derivatives on gross behavior of animals whereas Brine shrimp lethality test involves testing lethality to brine shrimp nauplii which is recommended for screening of plants for general bioactivity.

1.6.2 Specific Bioassays:

These are specialized BA and yield information on specific bioactivity and could be used as secondary assays for fraction showing activity in the general BA. These assays may either use lower organisms, cellular/sub cellular systems, enzymes, intact cells or isolated tissues.

Table 1.1 List of Cellular/Subcellular Assays:

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<tr>
<th>Assay</th>
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<td>Trypsin inhibition</td>
<td>Anti-inflammatory, Antiviral</td>
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<tr>
<td>DPPH scavenging</td>
<td>Antioxidant</td>
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<tr>
<td>Antimicrobial</td>
<td>Infectious conditions</td>
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<tr>
<td>Amylase inhibition</td>
<td>Obesity, diabetes</td>
</tr>
<tr>
<td>Monoamine oxidase</td>
<td>Hypertension, Depression</td>
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1.6.3 Primary Screening Bioassays:

These are relatively simple, with the main objective to discover large number of bioactive molecules in the lab itself. e.g. Brine shrimp lethality trial, antibacterial trials, crown gall tumour inhibition trial.

Physical methods of analysis like chromatography are of limited use, since they can be used to detect/quantify a select group of compounds. By utilizing in-vitro BA, extracts can be tested as a whole
and the biological response can be expressed as ED$_{50}$, IC$_{50}$ etc. (quantal response) with 95% buoyancy interval. Aberration from the standard values can be an indication for derisory worth. Also, when an extract is tested in a BA, both the known and unknown bioactives express their effect to influence the assay results. However in a chemical assay only the known bioactives can be assayed; the unknown ones are generally ignored.

*In-vivo* studies are relevant to clinical conditions and also provide toxicity information, intricate designs, complications in determining mode of action are among some of their disadvantages. *In-vitro* studies on the other hand are faster and use relatively small amounts of materials. The pharmacological evaluation of extracts and pure isolated compounds is an essential aspect of drug discovery process and developments in the area of *in-vitro* techniques have substantially transformed this facet of natural product chemistry.