CHAPTER 1

INTRODUCTION

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During past two decades there has been a significant interest in the use of herbal medicines. World Health Organization has issued guidelines for assessment of quality, safety and efficacy of these medicines and emphasized on the need of standardized preparations for health benefits from consumer and health care point of view. The botanicals employed in herbal medicines should be well authenticated and documented. Desirability of good manufacturing practices, knowledge of active and characteristic constituents, standardization of manufacturing process, identification of active or characteristic substances by chromatographic printing to ensure consistence quality of the preparation are some of the approaches suggested for quality and safety of medicaments. Physical and chemical stability of the product, establishment of shelf life and studies from standpoint of pharmacological and toxicological activities may provide further strength in safety of herbal drugs. A country like ours, which have a very strong tradition in Ayurvedic, Unani and Siddha medicine can be beneficial of renewed global interest in herbal medicine by taking extensive research work in standardization and quality control of herbal products. Drugs affecting CNS are high demand areas where herbal medicine may contribute substantially.

Complementary and Alternative Medicine (CAM) as it is called outside India and traditional medicine as it is referred to by the World Health Organization, is rapidly growing in economic importance worldwide. In many parts of the world, people are becoming concerned about the adverse effects of chemical drugs and the escalating cost of conventional health care. Longer life expectancy and life style related problems have brought with
them an increased risk of developing chronic, debilitating diseases such as mental disorders. Although new treatments and technologies for dealing with them are plentiful, more and more patients are now looking for simpler, gentler therapies for improving the quality of life and avoiding iatrogenic problems. According to WHO, a significant percentage of people are using traditional medicine and expenditure on traditional medicine is increasing day by day. The world market for herbal medicine including herbal products and raw materials has been estimated to have an annual growth rate of between 5 and 15%. In a wider context, there is a growing demand for plant based medicines, health products, pharmaceuticals, food supplements, cosmetics etc. in the national and international markets. The global market in herbal products is over US $ 60 billion per year. India at present exports herbal material for medicines to tune of Rs 446.3 crores only which can be raised to Rs 3,000 crores by 2005 (Handa, 1991, Murthy, 2000). China and India are two great producers of medicinal plants, having more than 40% of global biodiversity. In India, more than 1,800 plants belonging to different families are used for their therapeutic efficacy (Chatterjee, 1997). China, besides meeting its domestic requirement, is earning US $ 5 billion per year from herbal trade but unfortunately India's share in the global trade of herbals is very poor due to lack of quality control and standardisation measures (Bhutani, 2000). If India wants to emerge as a major player in global herbal products based medicine, it requires a grand strategic plan particularly in standardisation and quality control of herbal drugs to boost the export to Rs 10,000 crores by 2010 and can minimize the import (De, 1993 and Chakravarthy, 1993).

1.1 STANDARDISATION

The importance of standardisation of herbal drugs is now well understood by the consumer as well as the industry. Standardization helps in
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effective quality control during commercial production of such drugs since pharmacological standards are not adequate in most cases. In the past, the Ayurvedic physician would himself prepare small quantities of medicines for his patients but due to commercialization, the need for standardization has become important and necessary (Handa et al., 2003 and WHO, 1999).

During last two decades or so, emphasis has been laid on chemical methods of standardization based on physical, chemical assays, chromatographic analysis and various spectroscopic methods. Most of these are qualitative methods, though many plant materials have been standardized quantitatively using HPLC & HPTLC and these methods are used as an effective quality control parameter. In such cases, chemical markers have been isolated and characterized. In several plant materials spectroscopic methods of standardization have also been found to be useful. However, marker compound based standardization in many cases has not been as effective since these markers are not biologically active constituents in most of cases (WHO, 2001).

All these methods account for a single chemical entity or group of chemical compounds, but in many plants the activity may be attributed to different types of compounds that act synergistically to show the desired biological activity. Therefore, standardization by chemical methods, although used widely may not prove to be a complete way of standardization.

Sometimes the use of bioassay has been found to be an effective method in standardization and quality control of herbal materials. Though this method of standardization is not yet popular as compared to chemical methods, the trend all over the world is now on use of biological assay methods in addition to chemical methods, which ensures consistent clinical efficacy of the herbal product from batch to batch.
1.2 CNS AND HERBAL DRUGS

The Central Nervous System is the most complex and highly organized of all the biological systems. It is fascinating how the billions of brains and spinal cord cells work together to control the various functions of organs and systems in the body. The activity and function of the CNS are subject to a wide range of chemical influences, which are capable of producing a sequence of effects. The CNS consists of the brain & spinal cord and serves to coordinate and direct the functions of all body tissues. It is only the control, which enables the organism to adapt to a constantly changing environment (homeostasis).

Herbal medicines acting on CNS are becoming increasingly popular among consumers, the increasing demand for herbal medicines inevitably led
to the issue of obtaining and maintaining their quality. As a result, there has been a tremendous quality consciousness for the herbs acting on mental health in countries like USA, member countries of European Union, China and Australia etc. Unfortunately however, in Indian concept of quality did not get much attention. Hence, the Indian Council of Medical Research (ICMR) has adopted a standardization-oriented strategy for validating the claims of efficacy of traditional herbal remedies acting on CNS.

1.3 MENTAL HEALTH

Mental Health forms an extremely important plank of the Indian system of medicine viz. Ayurveda. It is defined as a state of sensorial, mental, intellectual and spiritual well being. In the Ayurvedic system of medicine working is done under the principle of tridosha i.e. vata, pitta and kapha. The later two are roughly synonymous to stimulant and sedative activity respectively. Mental disease in Ayurveda differs from the mental diseases as understood by the modern medicine. Disease like insanity, schizophrenia, hypochondria, melancholia, paranoids etc. which are partly mental and partly physical. In Ayurveda the humans are divided into three psychosomatic types, namely the vata-prakriti, pitta-prakriti and the kapha-prakriti. The varieties of human physique and the varities of temperament has divided humans into three basic types ecotomorphs, mesomorphs and endomorphs. Since medicine in Ayurveda covers every thought, action, word, experience and substance that exists in the world, there is nothing we can think of that shall not fall into one of the three categories of the vatic, paittic and kaphaic kingdoms. Thus the sun is paittic and the shade is khaphaic or vata kaphaic in nature. A stimulant is a paittic drug and a sedative is a khapaic drug. An alcoholic drink, being paittic, will increase the paittic activity in the body and the antipaittic or kaphaic coconut water will counter the action.
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Medicinal plants are an important element of indigenous medical system in India as well as in other countries. Medicinal plants have been used to alleviate human suffering for thousands of years. Even today, about 80% of world population, mostly in emerging and developing countries of Asia, Africa and Latin America rely on medicinal plants for their primary health care. Herbal remedies gained popularity due to their effectiveness, easy availability and comparative freedom from serious toxic effects.

1.4 CLASSIFICATION OF CNS ACTING HERBAL DRUGS

CNS acting herbals may be classified on the basis of their pharmacological and therapeutic potential.

CLASSIFICATION OF CNS ACTING HERBAL DRUGS

1. Tranquilizers
   i. Acorus calamus
   ii. Celastrus paniculatus
   iii. Sesi sibiricum
   iv. Paspalus scrobiculatum
   v. Morus indica
   vi. Convolvulus pluricaulis

2. Neuroleptics
   i. Bacopa monniera
   ii. Acorus calamus
   iii. Sausurea lappa
   iv. Fumaria indica

3. Anticonvulsants
   i. Cinchorium intibus
   ii. Selinium veginatum

4. Psycho-stimulants
   i. Bacopa monniera
   ii. Cissampelos pareira
   iii. Convolvulus pluricaulis
   iv. Melia azedarach

5. Adaptogens
   i. Withania somnifera
   ii. Ocimum sanctum
   iii. Cicer arietinum
   iv. Cansoora diffusa

6. Sedatives
   i. C. paniculatus
   ii. Ocimum sanctum
   iii. Melia azedarach
1.5 QUALITY CONTROL AND STANDARDISATION OF HERBAL DRUGS

The World Health Organization (WHO) encourages, recommends and promotes traditional/herbal remedies in national health-care programmes because these drugs are easily available at low cost, comparatively safe and people have faith in them. Herbal drugs (herbal medicinal products) represent a substantial proportion of the global drug market and in this respect internationally recognized guidelines for their quality assessment are necessary. The WHO Assembly in a number of resolutions has emphasized the need to ensure quality control of medicinal plant products by using modern techniques and applying suitable standards and has published quality control methods for medicinal plant material (WHO, 1979).

The single and most important factor standing in the way of wider acceptance of herbal drug is the non-availability or inadequate standards of checking quality by modern methods. This also hinders modernization or modification of production methods, as there is no way to establish the equivalence of the product made by the modified method with the original. The main reason advanced for the difficulty in developing quality control standards is that most of these products use whole herbs, or parts of plants or their total extracts, and in many cases a mixture of a number of plants. These drugs quite often contain a varied number and quantity of chemical constituents. It is challenging to develop suitable standards because a vegetable drug or preparation thereof is regarded as one active entity in its entirety, whether or not the constituents with therapeutic activity were known. Standardization of a herbal drug is not just an analytical operation ending with identification and assay of an active principle. Rather, it embodies total information and controls necessary to guarantee composition consistency (WHO, 1991).

Standardization of the presumed active compounds of a plant drug in general does not reflect the reality since only in a few cases drug activity does
depend upon a single component. Generally, it is the result of concreted activity of several compounds, some in isolation and inert but contributing to the activity of the plant. Although these inert components do not directly affect pathological mechanism, it is reasonable to use the complex mixture of components provided by a medicinal plant because the inert components might add to the stability of active components and influence their bioavailability and excretion. If different active compounds are present in a plant drug, they might have additive or potentiating effect.

Directives on the analytical control of a plant drug must take into an account the fact that the plant material has a complex composition. Therefore, the analytical limits cannot be set as precisely as for the pure chemical compound. Plant drugs are inevitably inconsistent and their composition is influenced by several factors such as age of the plant, geographical source and climate, harvesting period, method of drying, storage period and conditions. To eliminate some of the causes of inconsistency, use should be made of cultivated rather than wild plants which are often heterogeneous with respect to above factors and consequently in their content of active principle. All these factors make standardization of herbal medicinal products a difficult task, requiring innovation while applying modern techniques to develop standards for medicinal plants and their products (WHO, 1998).

Consistent quality of herbal medicinal products can be assured if the starting materials are defined in an explicit and rigorous manner. Each plant used for processing should be botanically identified and checked using its pharmacognostic chemotaxonomic characteristics. Comparison of a sample from raw material with herbarium specimens maintained in a manufacturing house repository can prove useful. The geographical source, season of collection, method of drying, parts of the plant used, whether fresh or dried, should be recorded.
1.6 WHO GUIDELINES FOR THE ASSESSMENT OF HERBAL MEDICINES

In 1991, WHO published guidelines for the assessment of herbal medicines. The objective was to define the basic criteria for the evaluation of quality, safety and efficacy of herbal medicines and thereby help national regulatory authorities, scientific organizations and manufacturers undertake assessment of the documentation/submission/dossiers of such products. The guidelines also provide details on the preparations of the documentation and data for the assessment of herbal medicines and address the following points:

- Assessment of quality including pharmaceutical assessment, crude plant material, plant preparation, finished products and stability.
- Assessment of safety including toxicological studies and documentation of safety based on experience.
- Assessment of the efficacy including activity, evidence required to indications and combination products.
- Intended use including product information for the consumer and promotion.

The guidelines suggest classification of herbal remedies into two groups; those with well established traditional use and newly developed products. It was recommended that the requirements for assessment of these two groups should be different. As a general rule, traditional experience means long term use, as well as medical, historical and ethnobiological background of the product. Depending on the history of the country, the long-term use may vary but would be of at least several decades (WHO, 1997).

The guidelines suggest that all the necessary approaches should be taken to ensure correct identification of plants. It is noted that when identification of an active principle of herbal medicine is not possible, it should be sufficient to identify a characteristic substance or mixture of substances to ensure consistent quality of herbal medicines. All herbal
procedures should be carried out in accordance with Good Manufacturing Practices (GMP).

On safety assessment, these guidelines suggested (WHO, 1996):

- All relevant aspects of the safety assessment of a medicinal product should be covered.
- No specific restrictive regulatory action should be undertaken for a traditionally used product without demonstrated harm unless new evidence demands a revised risk-benefit assessment. Documents submitted should provide evidence on long-term use.
- For drugs used over a long period, chronic toxicological risks may have occurred but may not have been recognized.
- If long-term traditional use cannot be documented, or there are doubts on safety, toxicity data should be submitted.
- If any toxicological studies are available, they should form part of the assessment. A review of relevant literature should be provided with original articles or references to the original articles.

1.7 BIOPHARMACEUTICAL CHARACTERIZATION OF HERBAL MEDICINAL PRODUCTS

1.7.1 General Considerations

In contrast to chemically defined drug products, the biopharmaceutical quality and behaviour of herbal medicinal products (HMPs) often are not well documented. In most cases in-vitro/in-vivo biopharmaceutical characterisation is complicated by the complex composition of herbal drug preparations, extensive metabolism of constituents and the resulting analytical difficulties. The active pharmaceutical ingredient (API) of HMPs is generally defined to be the whole herbal preparation, e.g. the extract in its entirety. Individual or
groups of constituents have only in selected cases been identified to be responsible for the therapeutic activity. The existing tight network of rules concerning dissolution testing and investigation of bioequivalence has not yet completely been transferred to HMPs. The first signs are USP drafts of monographs on dietary supplement products that include dissolution testing and an EMEA proposal on guidance on specifications for HMPs.

In most cases there is no doubt that a complete and rapid dissolution of the whole plant extract is a prerequisite for clinical efficacy of HMPs. Some lipid and essential oil herbal drug formulations will however not dissolve completely.

1.7.2 Chemical Composition and Classification of Active Pharmaceutical Ingredients in HMPs as a prerequisite for Biopharmaceutical Characterization

As the whole herbal drug preparation, e.g. extract, is regarded as the active pharmaceutical ingredient (API), several extract types, depending on the pharmaceutical analysis, pharmacological toxicological and clinical findings, can be identified:

A. Extracts containing constituents (single or groups) that are solely responsible for the known and acknowledged/well documented therapeutic activity. Adjustment (standardisation) to a defined content is acceptable using inert excipients or preparations with a higher or lower content.

B1. Extracts containing chemically defined constituents (single or groups) possessing relevant pharmacological properties (active markers). These substances are likely to contribute to the clinical efficacy, however, evidence that they are solely responsible for the clinical is not yet available (e.g. extracts of Ginkago, St. John’s Wort). The
characterisation of these extracts should take into consideration as far as possible the particular state of knowledge concerning the documented efficacy, quality and safety of an extract. Standardisation by blending different lots of a herbal drug before extraction, or by mixing different lots of herbal drug preparation is appropriate. Adjustment using excipients is not acceptable.

B2. Extracts containing no constituents documented as being determinant or relevant for efficacy, or as having pharmacological or clinical relevance. In these cases, chemically defined constituents (markers) without known therapeutic activity, may be used for control purposes. These markers may be used to monitor good manufacturing practice or as an indicator for the assay/content of the drug product.

The classification implies that an extract may be progressed from type B2 to B1 and even to type A as further knowledge is acquired about the extract. The proposed classification seems to be useful to determine the scientific level and future efforts for biopharmaceutical characterisation of HMPs.

1.7.3 Special Aspects of HMPs Concerning Investigation of Bioavailability or Bioequivalence

HMPs are in many cases based on traditionally known herbal materials and preparations (extracts). Their use is often well established but not based on systematic pre-clinical and clinical studies. Traditional HMPs may show great differences in the type of extracts used (even from the same plant), the dosage forms and strengths. The role of bioavailability and bioequivalence (BA/AE), in the case of substitution of one product by another has not yet been classified.
In relatively few cases HMPs have been developed using documented pharmacological, toxicological and clinical experiments either from known traditional herbs or from herbs and indications not included in the acknowledged traditional use. These HMPs often contain concentrated or purified extracts in order to improve the dosage or to reduce the side effects. For new or technologically highly developed HMPs especially, the question regarding the requirements for a product intended to be substituted for the specific approved herbal medicinal product arises.

Pharmaceutical equivalence

HMPs are pharmaceutically equivalent if they contain the same quantity of the same active substance that comply with the same specifications in the same dosage form. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process may lead to faster or slower dissolution and/or absorption.

A strict interpretation of the above for HMPs would imply that extracts from the same plant are not pharmaceutical equivalent if manufactured by different methods and with different extraction solvents. Different formulations, using the same extracts (e.g. coated tablets or soft gelatine capsules, even immediate release) may also not automatically be regarded as pharmaceutical equivalent. Therefore, the significance of the same specification is of great importance.

Essentially similar products

A proprietary medicated product is essentially similar to another product if it has the same qualitative and quantitative composition in terms of active substances and the pharmaceutical form is the same and, where necessary, bioequivalence with the reference product has been demonstrated
by appropriate bioavailability studies. By extrapolation, for immediate release products, the concept of essentially similarity also applies to different oral forms (e.g. tablets and capsules) with the same active substances.

An essentially similar product is intended to be substituted for an innovator product. An innovation product is a medicinal product authorised and marketed on the basis of a full dossier i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data.

In the case of HMPs and plant extracts essential similarity is determined by the manufacturing process (product by process). Essential similarity may be assumed if the production methods and the specification are the same or essentially the same.

To ensure pharmaceutical equivalence (essentially similar composition) the specified herbal material, the drug preparation with the drug : extract ratio (DER) and the principal extraction method (mainly the primary extraction solvent), must be used. Extracts are more equivalent, the more the constituents are qualitatively and quantitatively congruent.

Essentially similar extracts must correspond regarding all their constituents. Their fingerprints should match qualitatively and quantitatively is most important especially if efficacy and safety have been demonstrated with an individual plant extract in its specific composition.

Therapeutic equivalence

A medicinal product is therapeutically equivalent to another product if it contains the same API and clinically shows the same efficacy and safety as that product of which the efficacy and safety has been demonstrated.

For chemically defined substances, demonstration of comparative bioavailability or bioequivalence is generally the most appropriate method of
substantiating therapeutic equivalence between medicinal products which are pharmaceutical equivalents or alternative, provided they contain only excipients that are generally recognised as not having an influence on safety and efficacy.

Therapeutic equivalence of HMPs may in many instances be demonstrated either by the biopharmaceutical classification system (BCS) or clinical studies rather than bioequivalence studies. Under certain circumstances BCS data on the API (plant extracts or constituents relevant for efficacy) may qualify for a bioavailability/bioequivalence study waiver. In many cases however studies are required to demonstrate therapeutically equivalence.

1.7.4 *In vitro* Dissolution Testing of Herbal Medicinal Products

*In vitro* dissolution testing is performed to determine the rate quantity of drug substances dissolved in a specific time. It is an important tool to characterise the biopharmaceutical quality of finished drug products during development and to control the quality of marketed products. Comprehensive guidelines for dissolution testing of solid oral products have been established by FIP (FIP-guidelines, 1997).

**Acceptance Criteria**

In accordance with the FIP proposal, disintegration instead of dissolution testing may be sufficient for rapidly dissolving products containing herbal drug preparations that are highly soluble throughout the physiological pH range. Acceptance criteria with a single point measurement are appropriate for immediate release drug products. Multiple point acceptance criteria are necessary for modified release dosage forms.

Procedures and acceptance criteria should be set on the basis of bioavailability/bioequivalence (BA/BE) studies and in vivo dissolution data
calculated from plasma concentrations measured in clinical studies. However, for HMPs relevant data are not available in published literature. For setting specifications, the physico-chemical properties, e.g. the solubility and permeability of the API summarized in the Biopharmaceutical classification system (BCS) are useful. Three categories of immediate release HMPs containing different types of API (extracts) have to considered in dissolution testing:

A. Extracts containing constituents with known and acknowledged therapeutic activity, solely responsible for the clinical efficacy. The API is adjusted (standardised) to a defined content of the active compound. The dissolution test is feasible. The quality of the individual product must be documented.

B1. Extracts containing chemically defined constituents (single or groups) possessing relevant pharmacological properties (active markers). It is likely that these substances contribute to the clinical efficacy. The dissolution test is feasible for active markers. The choice of active markers for dissolution testing has to be justified with respect to the particular state of knowledge concerning efficacy, quality and safety of an extract.

B2. Extracts where no constituents at all are acknowledged as being determinant or relevant for efficacy, or as having pharmacological or clinical relevance. The dissolution test is not applicable for selected constituents. The dilemma of dissolution testing of HMPs in general is that only selected constituents can be traced but not the whole extract as API.

1.7.5 Relevance of the Biopharmaceutical Classification System for HMPs

The Biopharmaceutical classification system (BCS), which was originally developed for chemically defined synthetic drug substances may be helpful for HMPs as well (Blume et al., 2000). The BCS takes into account the physicochemical characteristics of a compound, in particular their solubility
INTRODUCTION

(in aqueous buffer systems of physiological pH) and permeability (through gastrointestinal membranes). According to this BCS, APIs are classified into four groups (group I high solubility, high permeability; group II low solubility, high permeability; group III high solubility, low permeability; group IV low solubility, low permeability). In this context high solubility is defined such that the highest dosage strength is soluble (>90%) in 250 ml buffer and high permeability if more than 80% of the dose is absorbed after oral administration.

According to BCS a waiver of BA/BE studies is granted for Class I drugs. In extension a waiver was also proposed for Class III drugs (Blume et al., 1999). Some BCS principles were recently integrated into the note for guidance on the investigation of bioavailability and bioequivalence concerning immediate release forms. In order to justify the waiver of in vivo bioequivalence studies the following characteristics should be considered according to the note for guidance.

Characteristics related to the active substance

• Risk of therapeutic failure or adverse reactions.
• Risk of bioequivalence
• Solubility, highest dosage strength in 250 ml of each of three pharmaceutical buffers (preferably at pH 1.0, 4.6, 6.8).
• Pharmacokinetic properties.

Characteristics related to the medicinal product

• Rapid dissolution (85% are dissolved within 15 minutes).
• Excipients
• Manufacture

The note for guidance reflects that the investigation of the solubility and the rapid dissolution of the API is of superior importance than the permeability of the active pharmaceutical ingredient.
It seems scientifically acceptable that bioavailability of an active ingredient depends on solubility as well. However, only solubility/dissolution may be pharmaceutically controlled and influenced (e.g. by the pharmaceutical formulation). Therefore for "immediate release" herbal medicinal products the solubility of the total extract and known pharmacological active constituents are crucial parameters for a waiver of bioequivalence or clinical studies.

**TABLE 1.1: PLANTS CLAIMED FOR CNS ACTIVITY** (Dandiya, 1990)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>PLANTS</th>
<th>REPORTED CONSTITUENTS</th>
<th>PHARMACOLOGY</th>
<th>THERAPEUTIC USES</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.</td>
<td><em>Par��um scrobiculatum</em> (Hirik)</td>
<td>(i) Henriciacontanol (ii) Henriciacontanone (iii) Sitosolol</td>
<td>(i) Tranquilizer (ii) Hypothermia</td>
<td>(i) Schizophrenia  (ii) Psychosis  (iii) Anxiety</td>
</tr>
<tr>
<td>4.</td>
<td><em>Seseli sibricum</em> (Bhootkeshi)</td>
<td>(i) Volatile fraction from aerial parts (ii) Sesebrinic acid</td>
<td>(i) Sedative  (ii) Tranquilizer  (iii) Analgesic</td>
<td>(i) Anxiety</td>
</tr>
<tr>
<td>8.</td>
<td><em>Convolvulus pluricaulis</em> (Shankpushpi)</td>
<td>(i) Shankhpushpine</td>
<td>(i) Motor activity ↓ (ii) Mild hypnotic (iii) Mild analgesic (iv) Anti-seizures</td>
<td>(i) Anti-anxiety</td>
</tr>
<tr>
<td>S.No.</td>
<td>PLANTS</td>
<td>REPORTED CONSTITUENTS</td>
<td>PHARMACOLOGY</td>
<td>THERAPEUTIC USES</td>
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<td>----------------------------------</td>
</tr>
<tr>
<td>9.</td>
<td>Melia azedarach</td>
<td>(i) Quercetin (ii) Rutin (iii) Bakayanin (iv) Bakalactone</td>
<td>(i) CNS stimulant (fruits) (ii) Anorexogenic activity (iii) Mild analgesic (iv)</td>
<td>Nervous headache</td>
</tr>
<tr>
<td></td>
<td>(Bakain)</td>
<td>(v) Tetratriterpenoid (vi) Catechin (vii) Anthraquinone</td>
<td>Mild potentiation of pentobarbitone induced hypnosis in mice</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pigments (viii) Kaempferol (ix) 3-O-β-rutinoside (x) Limonooids</td>
<td>(i) Anticonvulsant (ii) Physical power and swimming endurance in mice ↑ (iii)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(xi) Melatoxins</td>
<td>Non-specific resistance during stress ↑ (iv) Modulator of serum trace elements ↓</td>
<td>(i) Trigeminal neuralgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(v) Anti-neoplastic</td>
<td>physical power and endurance in</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>human (ii) Anti-anxiety (iii)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Adaptogenic</td>
</tr>
<tr>
<td>10.</td>
<td>Withania somnifera</td>
<td>(i) Nicotine Somniferin (ii) Somniferine (iii) Somine (iv)</td>
<td>(i) Physical endurance and survival time (ii) Prevented stress induced ulcers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Ashwagandha)</td>
<td>Withanine (v) Withanamine (vi) Sitoindosides IX &amp; X</td>
<td>in rats (iii) CC₄ hepatotoxicity in rats and mice ↓ (iv) Milk induced Leucocytosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(vii) Withanolide (viii) Sitoindosides VII &amp; VIII (ix)</td>
<td>in mice ↓ (v) Haemagglutination &amp; Ig E antibody titre ↑ (vi) Antigen induced</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withanolide-D</td>
<td>hist. release (inhibition) ↓ (vii) Apomorphine fighting↓ (viii) Despair immunity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(ix) Synergism (Bromocryptine)</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Ocimum sanctum</td>
<td>(i) Eugenol (ii) Nerol (iii) Caryophylline (iv) Luteolin</td>
<td>(i) Non-specific assistance during stress ↑ (ii) Viral encephalitis (Survival</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Tulsi)</td>
<td>(v) Orientin (vi) Molludin</td>
<td>time of patients ↑) (iii) Adaptogenic (iv) Modulator of immune response</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Cicer arietinum</td>
<td>Pangamic acid</td>
<td>Anti-stress activity</td>
<td>Adaptogenic</td>
</tr>
<tr>
<td></td>
<td>(Chana)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Canesora diffusa</td>
<td>Diffutin</td>
<td>Psychoneurological</td>
<td>Adaptogenic</td>
</tr>
</tbody>
</table>

1.8 RESEARCH ENVISAGED AND PLAN OF WORK

_Evolvulus alsinoides, Convolvulus pluricaulis, Centella asiatica and Bacopa monniera_ are the important traditional drug in Ayurvedic and Unani system of medicine. Because of their utility in our traditional system of medicine it has been extensively investigated by the research workers.

The pharmaceutical activities of _Centella asiatica_ and _Bacopa monniera_ are considered to be due to several saponin constituents namely asiaticoside,
asiant acid, madecassoside and madecassic acid (Karting, 1988). The therapeutic potential of *Evolvulus alsinoides* and *Convolvulus pluricaulis* is considered to be due to tannins and alkaloids (Basu and Dandiya, 1948).

The literature review on these plants revealed that most of the work undertaken by researchers was related to pharmacological screening of different extracts of plants. Much attentions has not been paid so far for the standardization and estimation of active components present in the plants and none of the research literature has revealed the attention on the development and standardization of polyherbal formulations acting on Central Nervous System.

Since ancient times, a number of herbal medicines have been used in the treatment of CNS disorder and many studies have been carried out in the search of suitable plant drugs and their multiherbal formulations that would be effective in improving the performance of CNS. There is an increase in demand of the natural products for treatment of CNS disorders.

In Ayurvedic treatment, a medicine consists of plant products, either single drug or in combination with other (polyherbal formulation) are considered to be less toxic and free from side effects as compared to synthetic drugs.

Despite considerable progress in the treatment of CNS disorder by synthetic or herbal formulations, search for new drugs continues as the existing synthetic or herbal drugs have several limitations. In this context polyherbal formulations hold promise in the management of activity on CNS. In the present study, a survey of Ayurvedic literature reveals that the activity of *Evolvulus alsinoides, Convolvulus pluricaulis, Centella asiatica, Bacopa monniera* have been successfully used in Ayurvedic and other traditional formulations and found to be efficacious and cheap, as compared to synthetic drugs, but not evaluated systematically.
INTRODUCTION

The associated disadvantages with existing formulations stimulated the research to establish natural resources eliciting the activity on CNS and to investigate the traditional medicine with proper chemical and pharmacological profiles.

Thorough literature survey provoked to undertake the study involving standardization of crude drugs, extraction and phytochemical investigation, pharmacological screening of extracts and its formulations and development of polyherbal formulations. This kind of detailed scientific study has not been documented so far. Hence, it was worthwhile to carry out the development and standardization of polyherbal formulation for some drugs acting on CNS.

PHASE-1: COLLECTION AND AUTHENTICATION OF CRUDE DRUGS

- The crude drugs of Centella asiatica, Bacopa monniera, Evolvulus alsinoides and Convolvulus pluricaulis were collected and authenticated for their correct botanical identity.
- The drugs were then shade-dried, powdered to 40 # mesh particle size and stored in air tight containers.

PHASE-2: STANDARDIZATION OF CRUDE DRUGS

- The powdered materials of all crude drugs were subjected to standardization with various physical and chemical parameters.

PHASE-3: EXTRACTION OF CRUDE DRUGS

- About 5 kg of each of standardized crude powder depending on the extractive values was subjected to extraction by maceration using various solvents such as Methanol, Petroleum ether, Chloroform and Water etc. The extracts were filtered and concentrated under reduced pressure.

PHASE-4: PHARMACOLOGICAL SCREENING OF EXTRACTS

- The standardized extracts were subjected to pharmacological screening employing following screening models
1. Elevated plus maze.
2. Two way active avoidance with negative (punishment) reinforcement: shuttle-box.
3. Measurement of pentobarbitone induced sleep.
4. Spontaneous motor activity.

**PHASE-5: STANDARDIZATION OF EXTRACTS**

- The concentrated extracts of all the crude drugs were subjected for quality control and standardization with various physical and chemical parameters.

**PHASE-6: ISOLATION, ESTIMATION AND CHARACTERIZATION OF MARKER COMPOUNDS**

- Fluorescent producing (at 365 nm) components from methanolic extracts of *Evolvulus alsinoides* and *Convolvulus pluricaulis* were isolated by preparative Thin Layer Chromatography.
- Isolated markers were subjected for characterization by elemental analysis, IR, FAB-MASS, $^{13}$C NMR and $^1$H NMR.
- The quantitative estimation of isolated markers, asiatic acid and bacoside-b was undertaken by HPTLC and HPLC.

**PHASE-7: DEVELOPMENT AND EVALUATION OF HERBAL FORMULATIONS**

- Most active extracts i.e. methanolic extract of *Centella asiatica*, *Bacopa monniera*, *Evolvulus alsinoides* and *Convolvulus pluricaulis* were subjected for development of polyherbal formulation of solid and liquid dosage form.

**PHASE-8: STABILITY STUDIES OF POLYHERBAL FORMULATIONS**

- Tablet and syrup formulations were evaluated for their stability for the period of three months.
REFERENCES


