GENERAL INTRODUCTION

This chapter describes a brief historical background of medicinal plants and traditional system of medicine; natural products and drug discovery and a brief insight into Computer Aided Drug Design. The chapter also covers briefly about the family Scrophulariaceae, general description and distribution of Scoparia dulcis L., the plant’s botanical description, taxonomic classification and ethnomedicinal uses of different parts of this medicinal herb.

1.1 Historical background of medicinal plants and traditional system of medicine

Nature has been a source of medicinal agents for ages and remarkable quantities of modern drugs have been isolated from natural sources based on the traditional system of medicine (Durga et al., 2009). Historically, all therapeutic preparations were derived from plants (Ayyanar and Ignacimuthu, 2009). According to global estimation, 80% of about 4 billion population cannot meet the expense of the products of the Western Pharmaceutical Industry and thus reliant on traditional medicines. This system has been extensively practised on several accounts, such as population rise, scanty supply of drugs, excessive rate of treatments, side effects of numerous allopathic medications and improvement of resistance to currently used drugs for various infections that have led to increased emphasis on use of plant based drugs for varied human ailments (Goyel, 2005). Despite of overwhelming impacts and tremendous improvements of synthetic drugs, a huge fragment of the world populations still rely on drugs from medicinal plants (Joy et al., 2001).

Among the major indigenous systems of medicines such as Ayurveda, Siddha, Unani and Folk medicines, Ayurveda is the most established and extensively practised system
and has been an important part of Indian culture. It is gaining eminence as the natural system of health care all over the world which is based on the perceptions of scientific explanation. It is not only the science of treatment of the ill but also shields the entire gamut of happy human life involving physical, metaphysical and spiritual aspects. In the countries like Tibet, Mongolia and Thailand, the traditional system of medicine appears to be derived from Ayurveda and also being practised in Nepal, Bhutan, Sri Lanka, Bangladesh and Pakistan (Joy et al., 2001).

Among ancient civilizations, India has been recognized as a rich source of medicinal plants. The forest in India is the key repository of enormous quantity of medicinal and aromatic plants, which are largely collected as raw ingredients for the development of drugs and perfumery products (Thomas, 1997). Among 2,50,000 developed plant species on earth, over 80,000 are medicinal and approximately 15,000-20,000 plants have good medicinal properties, of which merely 7000-7500 species are used by traditional communities for their medicinal utilities. Even the Allopathic system of medicine has approved an aggregate of plant based drugs which form an important section of the modern pharmacopoeia (Joy et al., 2001).

Plant based drugs recommend a steady market globally and also imparts an essential basis for novel drugs. In most of the developing countries, the usage of plant drugs are growing because modern life saving drugs are beyond the reach of three quarters of the third world’s population while many such countries expend 40-50% of their total wealth on drugs and health care. It is assessed that world market for plant derived drugs may comprise about Rs.2,00,000 crores. At present, Indian contribution is below Rs.2000 crores. Indian exportation of raw drugs has progressively grown up to 26% from Rs.130 crores in 1991-92 to Rs.165 crores in 1994-95. Hence, the increased use of plant drugs
may reduce the financial burden of developing countries in near future (Joy et al., 2001).

Green plants synthesize large number of secondary metabolites that are commercially significant and are used in pharmaceuticals for the development of modified derivatives with enhanced activity and reduced toxicity. Till date, about 121 plant drugs have been recognized for which no synthetic one is currently available. On the other hand, the separation and documentation of the active principles and elucidation of the mechanism of action of a drug is of utmost importance (Joy et al., 2001).

However, continuous supply of the source material is difficult due to various aspects which include ecological changes, traditional practices, varied geographic distribution, work cost, selection of the superior variety and over exploitation by pharmaceutical industries (Joy et al., 2001). Again, many valuable plants are being lost and many under the verge of extinction. About 50% of the tropical forests have already been destroyed whereas in India, forest cover is declining at an annual rate 1.5mha/year (Thomas, 1997). Thus, systematic conservation of medicinal plants, scientific investigation of traditional medicines and derivation of drugs through bio prospecting are of great importance.

1.2 Natural products and drug discovery

The term “natural products” may be defined as any chemical constituent isolated from plants, animals and microbes (Harvey, 2008), or any biological molecule, usually secondary metabolites and small molecules having molecular weight less than 1500 amu, produced by an organism which are not strictly essential for the survival of the organism and is distinct from the more prevailing macromolecules such as proteins,
nucleic acids and polysaccharides that constitute the basic mechanism of fundamental processes of life (Cannell, 1998).

Secondary metabolites are a very extensive group of metabolites without distinct boundaries or unifying definition. Secondary metabolism comprises the product of overflow metabolism due to nutrient constraint or shunt metabolites produced during idiophase, resistance mechanisms and regulator molecules. If a secondary metabolite does not possess any adverse influence on the producing organism at any stages of differentiation, morphogenesis, transport, regulation or transitional metabolism, it may be preserved for a comparatively prolonged period during which it may come to deliberate a selective advantage. Secondary metabolism thus offers a sort of testing ground where novel metabolites ensure the opportunity to exist without being eliminated and provide an advantage to the producing organism. This is supported by the fact that secondary metabolites are often unique to a specific species or group of organisms, while many acts as antifeedants, sex attractants or antibiotic agents and many have no obvious biological function (Cannell, 1998).

Natural products have been the basis of several active constituents of medicines. This is broadly recognised to be true when applied to drug discovery in ancient periods before the invention of high-throughput screening and the post genomic era. Till date, more than 80% of drugs have been derived from natural products or influenced by natural compound (Sneader, 1996). The data on sources of novel drugs from 1981 to 2007 have shown that more than half of the drugs approved since 1994 are based on natural products (Newman and Cragg, 2007). The recently approved natural product based drugs include elliptinium, galantamine and huperzine (from plants), daptomycin (from microbes), exenatide and ziconotide (from animals) and tigecycline, everolimus, telithromycin, micafungin and caspofungin (synthetic or semi-synthetic compounds).
They provide a wide range of therapeutic potentials and also a great diversity of chemical structures (Ganesan, 2008). Moreover, natural products are more readily absorbed than synthetic drugs (Harvey, 2008).

Natural products have influenced many developments in organic chemistry (Wilson and Danishefsky, 2006; Newman, 2008), leading to the advance of synthetic methodologies and probability of generation of analogues of original lead compound with enhanced pharmacological or pharmaceutical properties (Sunazuka, 2008). Natural product scaffolds have also been well documented as being privileged structures in relation to their capability to be the source of promising drugs. Such scaffoldings are being used as basis of compound libraries generated by combinatorial techniques (Ertl, 2008). With the application of different techniques to generate analogues and derivatives of natural products, it becomes possible to develop novel compounds that can be patented, even though the original structure was previously revealed (Harvey, 2008).

Isolation of natural products diverges from the more established biological macromolecules because of their small size and varied chemical diversity (Cannell, 1998). With the advances in fractionation techniques for isolation and purification, and in analytical techniques to determine the structures, screening of natural product mixtures has now become more compatible with the estimated schedule of high-throughput screening campaigns. According to Singh and Barrett (2006), isolation and elucidation of structure of pure bioactive compounds from fermentation broths is currently possible in less than two weeks. With developments in NMR techniques, complex structures can be elucidated with much less than 1 mg of compound. Quinn et al., (2008) has recognized that it is now possible to generate screening library of extremely diverse compounds from plants with previously selected compounds from Dictionary of Natural Products to be drug-like in their physicochemical parameters.
Several other approaches are also being explored in efforts to increase the speed and efficacy that can be advantageous to drug discovery (Harvey, 2008).

In spite of many advantages and previous successes, several pharmaceutical companies have reduced the practice of natural products in drug discovery screening. This may be associated with perceived disadvantages of natural products such as complications in access and supply, complexities in natural product chemistry, innate tardiness of working with natural products, concerns about intellectual property rights and the expectations related to the use of collections of compounds prepared by combinatorial chemistry methods (Lam, 2007; Singh and Barrett, 2006; Baker et al., 2007; McChesney, 2007; Rishton, 2008). However, more than hundred natural product derived compounds are presently under clinical trials and at least hundred such related projects are in preclinical development. Most of them have been derived from plants and microbial sources (Butler, 2008). There is, however, also increasing interest in developing products that comprise mixtures of natural compounds from traditionally used medicines and defined combination of constituents extracted from green tea (Veregen TM) has been approved by the FDA and has recently come on the market (Charlish, 2008).

1.3 Computer Aided Drug Design

Design, development and commercialization of a drug is a tedious, time consuming and cost intensive process (Kuhlman, 1997) and the cost associated with this has been increasing successively during the past thirty four years (Halliday, 1992). Moreover, during this process, a few candidates will be inspected in the clinic and only a small number will be marketed whereas the market for high value added compound is very competitive. The novel compound must offer enhanced qualities in order to be
worthwhile for commercialization. Also, there are serious hurdles concerning ease and cost of synthesis, patentability, safety and social need for the novel compound. Considering both the prospective to human health and enormous expenses in time and money on drug discovery, any tool or technique that will enhance the effectiveness of drug discovery enterprise will be highly recommended. Computer-aided drug design (CADD) is such a technique which can be used to raise the efficacy of the drug discovery process (Ooms, 2000).

In principle, the *in silico* drug discovery process comprises three phases, viz., target selection, lead identification and lead selection. Due to tremendous progresses in structural biology and information technology, structure-based Computer aided drug design has become a significant method in the multi-step process of drug discovery. As an evolving technology, Computer aided drug design increases drug development by making use of the accumulated information of prevailing drugs and diseases, combined with inter disciplinary inputs from other fields. This process widely uses mathematical models and simulation tools based on the evaluation of probable risks from drug safety and the experimental design of new trials (Street and Mayo, 1999; Carlson and McCammon, 2000; Veselovsky and Ivanov, 2003). During the early 1980s, structural biologists started to design rational drugs based on protein structures. The first development was in the mid-1980s and the first successful stories of computer-aided rational design of peptide-based HIV-proteinase inhibitors, were published by the early 1990s (Erickson *et al.*, 1990; Adam *et al.*, 2002). Thenceforth, CADD has become a dynamic technique in drug candidate screening (Anand *et al.*, 2003).

In the first place of structure-based CADD, the three dimensional structure of a target protein or nucleic acid is elucidated by X-ray crystallography (Varney *et al.*, 1994) or NMR (Dunbar *et al.*, 1994). Using already generated protein and nucleic acid databases,
new computational techniques utilize the 3D structure of unliganded target to design completely new lead compounds \textit{de novo}. Large virtual combinatorial libraries of compounds can then be screened computationally before proceeding to the effort and expense of actual separation and biological studies. The capability to dock large quantities of candidate molecules into the binding site of a target macromolecule is a vital constituent of lead generation in structure-based drug design (Kuntz, 1992; Good, 1995). The most extensively used computational docking program includes DOCK (Kuntz et al., 1982) and several other programs such as ADAM (Adam et al., 2001), AutoDOCK (Buzko et al., 2002), FlexX (Keseru, 2001), SLIDE (Hawkins et al., 2001) and other dock databases can score candidate molecules on the basis of their interactions with the designated site of target protein. The \textit{de novo} generation of ligands can be accomplished with programs including 3D-QSAR (Jozwiak et al., 2004), DISCO (Myers et al., 1994), GRID (Bitetti-Putzer et al., 2001), LUDI and MCSS (Bitetti-Putzer et al., 2001).

With the rapid propagation of biological and chemical information, CADD has been intensely reformatting research and development strategies in drug candidate identification. The accelerating amount of therapeutic candidates is in increasing demand on new technologies and strategies to rationalize the procedure of screening for safe and effective remedies. This has inspired the application of molecular approaches to identify and validate drug candidates successfully in recent years (Wang, 2005).

\subsection*{1.4 A brief description about the family Scrophulariaceae}

The family Scrophulariaceae is comprised of mostly herbs, occasionally small shrubs and climbers including approximately 269 genera and 5100 species (Qureshi & Bhatti, 2008). Recently, many genera have been transferred to other families within Lamiales,
Plantaginaceae, Orobanchaceae and several new families. Some species of this family are semi-parasitic (Hay Rattle, Lousewort), many of them are popular garden plants and several are well known weeds (Yisa, 2009). Members of the family Scrophulariaceae have a cosmopolitan distribution, majority of them are found in temperate areas, including tropical mountains. The family description is based on the name of the genus *Scrophularia* L. (Qureshi & Bhatti, 2008).

### 1.5 The Plant: *Scopia dulcis* L.

*Scopia dulcis* L. is a well-known ethnomedicinal plant belonging to the family Scrophulariaceae and is widely distributed in tropical and subtropical regions. The plant is found almost around the globe, mostly in European, African, American and Asian countries. It is commonly known as sweet broom weed (India), tpycha kuratu (Japan), vassourinha (Brazil) and escobilla (Peru) (Okhale *et al.*, 2010). Morphologically, the plant is small, branched, glabrous, leafy annual herb or shrub with erects or ascending branches. It comprises a diverse group of biochemical constituents such as, phenols, saponin, tannins, amino acids, flavonoids, terpenoids and catecholamines. Various parts of the plant possesses excellent pharmacological properties, such as, analgesic and anti-inflammatory activity, neurotrophic activity, antiviral activity, antimalarial activity, anticancer activity and antidiabetic activity (Rashid *et al.*, 2009). Traditionally, the plant has been used as a remedy for diabetes in India and Nigeria (Okhale *et al.*, 2010), hypertension in Taiwan and fever in Gambia. Brazilian folkloric use it against different ailments such as abortions, bronchitis, cardiopulmonary disorders, coughs, diabetes, earache, eye problems, fever, gastric disorders, hemorrhoids, hypertension, hyperglycemia, insect bites, jaundice, liver disorders, malaria, menstrual disorders, pain, upper respiratory disorders, skin problems, worms and wound infection (Rashid *et al.*, 2009). Indigenous tribes of Nicaragua uses leaves or whole plant decoction against
anemia, childbirth, blood cleansing, burns, cough, diarrhea, fever, heart disorders, headache, infections, insect bites and stings, itching, liver disorders, malaria, menstrual disorders, snakebite, stomach disorders, venereal disease and for general tonic (Okhale et al., 2010). The biochemical constituents present in the plant are supposed to be mainly responsible for the potential pharmacological properties of this plant (Rashid et al., 2009).

1.5.1 Botanical description of *Scoparia dulcis* L.

*Scoparia dulcis* L. is a small, leafy, annual herb, grows up to half meter, with serrated leaves and small, white flowers. The plant is profusely branched where the younger stems are 5-6 angled and glabrous, leaves three whorled and simple. The petioles are short or sub sessile, laminae broadly elliptic to oblancoolate, bases attenuate, margins serrate, tips acute, unicostrate, reticulate and the surfaces glabrous. The inflorescences is axillary cymes and 1-2 flowered. Flowers are ebracteate, ebracteolate, pedicellate, bisexual, actinomorphic, tetramerous and hypogynous. Calyx is apospalous, the sepals four, imbricate in bud and persistent. Corolla synpetalous, four fid, the tubes short, the lobes obtuse, subequal and white. Androecium polyandrous, stamens four, didynamous, epipetalous, the filaments filiform, attached to the base of corolla tube, anthers dithecal, subsagittate, dorsifixed, introrse and dehiscence longitudinal. Pistil one, ovary ovoid or globose, two carpelled, syncarpous, two loculed, the placentation axile, the ovules numerous on the enlarged placentae, the style subclavate and the stigma bifid. Fruit asepticidal capsule, globose, valves membranous, the margins inflexed, seeds many, obovoid and endosperm fleshy. The flowering period is from October to December and fruiting period is from November to January (Kyaw et al., 2006).
1.5.2 Taxonomical classification of *Scoparia dulcis* L.

According to Takhtajan 1997, the taxonomical classification of *Scoparia dulcis* L. is as follows:

Division: Magnoliophyta

Class: Magnoliopsida

Subclass: Asteridae

Order: Scrophulariales

Family: Scrophulariaceae

Genus: *Scoparia*

Species: *dulcis*

1.5.3 Ethnomedicinal uses of various parts of *Scoparia dulcis* L.

*Scoparia dulcis* L. is extensively used in the indigenous system of medicine and is found to be beneficial and effective. Different parts of this plant have been traditionally used in herbal medicine for different medicinal utilities as discussed below.

**Aerial Parts:** The aerial parts of the plant are effective in childbirth, coughs, diarrhoea, expectorant, fever and stomach ache.

**Entire Plant:** The whole plant is used as abortive, aches, anaemia, aphrodisiac, blennorrhagia, bronchitis, burns, childbirth, contraceptive, coughs, diabetes, diarrhoea, dysentery, expectorant, fever, gastric disorders, headache, haemorrhoids, hepatosis, hypertension, insect bites, intestinal worms, jaundice, liver disorder, malaria, menorrhagia, menstrual problem, pain, rash, snake bites, swelling, toothache, venereal disease and wounds.
**Leaf:** The leaf part is useful in abortive, anaemia, burns, childbirth, contraceptive, cough, diabetes, diarrhoea, eye ailments, fever, headaches, haemorrhoids, insect bites and stings, worms of intestine, kidney trouble, liver diseases, malaria, menstrual problem, migraines, snake bites, stomach disorders, ulcers, urinary tract disorders, venereal disease, vomiting and wounds.

**Root:** The root is widely used as abortive and in bronchitis, diarrhoea, dysmenorrhea, fever, jaundice, liver disorders, malaria, menorrhagia, menstrual problem, skin infections, stomach pains and warts (Technical Data Report for Vassourinha *Scoparia dulcis* L., 2002).
Fig 1.1: The plant *Scoparia dulcis* L.