CHAPTER 1
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Introduction

1.1. Phytochemicals

The interesting chemicals called 'Natural Products' are derived as a result of the phenomenon of biodiversity where the interaction among organisms and their environment is responsible for the formulation of the diverse complex chemical entities within the organism, which in turn enhance their survival and competitiveness (Nurmikko et al., 2005; Mishra et al., 2011). Since thousands of year's natural products have been playing a very important role in health care as well as prevention of diseases. Written evidence of the use of natural products for curing various diseases has been provided in the ancient civilization of the Chinese, Indians and North-Africans (Philipson, 2001). The most ancient health care system is Ayurveda which is practiced widely in India, Srilanka and many other countries (Chopra et al., 2002). The main classics including detailed descriptions of more than 700 herbs are Atharvaveda (around 1200 BC), Charak Samhita and Sushrut Samhita (1000-500 BC) (Dash et al., 2001). Documentation of use of natural products for medicinal application, in the Western world can be found as far back as 78 A.D., when Dioscorides wrote “De Materia Medica”, which describes thousands of medicinal plants (Tyler et al., 1988). Description of a number of medicinal plants that remain important in modern medicine has been included in this treatise and they continue to be used as crude drug preparation, as well as serve as the source of important pure chemicals which have become mainstays of modern therapy (Rout et al., 2009). However, the isolation of active components from various medicinal plants, by scientists was not done until the nineteenth century. It was Friedrich Serturner who isolated morphine from Papaver somniferum, in 1806 and since then the extensive screening of natural products for their medicinal purposes have been carried out.
World Health Organization (WHO), defines a medicinal plant as that which, in one or more of its parts contains any such substances that can be used for therapeutic purposes, or which serve as precursor for chemo-pharmaceutical semi synthesis. Parts of such plant, including leaves, stems, barks, flowers, roots, rhizomes, fruits, grains or seeds are used for controlling or treating a disease condition and as such may be the sources of medically or biologically active chemical substances. These non-nutrient chemical components or biologically active substances present in the plants are often referred to as phytochemicals (‘Phyto’ from Greek phyto meaning plant) or phytoconstituents and are responsible for protection of the plant from microbial infections or infestation by pests (Abo et al., 1999; Liu 2004; Nweze et al., 2004; Doughari et al., 2009). Biosynthesis and breakdown of proteins, fats, nucleic acids and carbohydrates, which is essential for the survival of all living organisms is known as primary metabolism, with the compounds involved in the pathways known as “primary metabolites” (Dewick 2002). On the otherhand the biosynthesis of compounds called secondary metabolites (natural products), which are generally not essential for the growth, development and reproduction of an organism, is referred to as “secondary metabolism”. It is often found to be unique to an organism or expresses the individuality of a species (Dewick 2002; Maplestone et al., 1992). Secondary metabolites produced within organisms assist in the survival of the organism either by helping the organism in adapting to its surrounding environment or by helping them in defending themselves against the predators (Dewick 2002; Colegate et al., 2008). The fundamental process of photosynthesis, glycolysis and Kreb’s cycle are involved in secondary metabolism to afford biosynthetic intermediates which results in the formation of secondary metabolites also known as natural products (Dewick 2002). The characteristic chemical structures that possess an array of biological activities are a result of the unique biosynthesis of natural products, produced by countless number of terrestrial and marine organisms (Dias et al., 2012). As per WHO, 80% of the people still rely on traditional plant based medicines for primary health care (Farnsworth et al., 1985) and 80% of 122 plant derived drugs are related to their
original ethno-pharmacological purpose (Fabricant et al., 2001). About 121 drugs that are prescribed in USA today come from natural products, 96 of which come either directly or indirectly from plant sources (Benowitz 1996). Forty-seven percent of the anticancer drugs in the market come from natural products or are natural product mimic (Newman et al., 2007). Further investigation of medicinal plants as potential medicines has been promoted by the knowledge associated with traditional medicine (complementary or alternative herbal products) and has led to the isolation of many natural products that have become well known pharmaceuticals (Dias et al., 2012). Various microorganisms, marine organisms, terrestrial plants, terrestrial vertebrates and invertebrates have been the source of natural products medicines (Newman et al., 2000) and their importance in modern medicine have been discussed in different reviews and reports (Newman et al., 2000; Newman et al., 2003; Koehn et al., 2005; Paterson et al., 2005; Balunas et al., 2005; Jones et al., 2006). The large proportion of natural product in drug discovery has stemmed from the diverse chemical structure and the intricate carbon skeletons of natural products. As natural products or secondary metabolites are being elaborated within living systems, these are often perceived of showing more biological friendliness and drug likeliness than totally synthetic compounds (Koehn et al., 2005), thus making such metabolites good candidates for drug development (Balunas et al., 2005; Drahl et al., 2005).

Recently, the field of research in natural products chemistry has received a great deal of interest owing to several factors, which includes the remarkable diversity in terms of both chemical structure and biological activities shown by diverse groups of naturally occurring secondary metabolites, unmet therapeutic needs, the utilisation of novel biologically active natural products as biochemical probes, the development of sensitive and novel techniques for detection of biologically active natural products, improved techniques for isolation, purification, and characterization of structure of these constituents and advancement in solving the demand for supply of complex natural products (Clark 1996; Rout et al., 2009). The use of plants as medicine involves extraction and isolation of biologically active components from the plants. Pharmaceutically,
the term extraction involves the separation of medicinally active components of plant tissues from the inactive inert components with the use of selective solvents through standard procedure. As the extraction proceeds, solvents diffuse into the solid plant material and solubilize components having similar polarity (Ncube et al., 2008; Tiwari et al., 2011). Attainment of therapeutically desired portions and the elimination of unwanted material by treatment with a selective solvent is the purpose of standardized extraction procedures for crude drugs (medicinal plant parts). The standardized extract thus obtained, may be used as such in the form of tinctures or fluid extracts for treating different diseases or may be further processed for incorporation in any dosage form. Such standardized medicinal plant extract contains complex mixture of many metabolites, such as alkaloids, glycosides, terpenoids, flavonoids and lignans (Handa et al., 2008). After extraction follows the isolation and the modern techniques for isolating the bioactive compounds involve different types of chromatography which are often guided by bioassays. Until 1950’s, determination of the structure of natural products were mostly done by degradative experiments and a structure was not proven until the compound had been synthesized in an unambiguous manner, also the stereochemistry was not often determined. Nowadays, structure elucidation is primarily done by spectroscopic techniques, and the stereochemistry is considered to be an important feature of the structure.

With the increasing interest and availability of a number of promising drug candidates which are of natural origin, in the current development pipeline, and with the lessening of technical drawbacks associated with natural product research, there are better opportunities for exploration of the biological activity of sources of natural products which were previously inaccessible. Additionally, the increasing acceptance of the fact that the chemical diversity of natural product is well suited for providing the core scaffolds for future drugs, there will be further developments in the uses of novel natural products and chemical libraries based on natural products in drug discovery campaigns (Doughari, 2012). Despite the increase in the use of medicinal plants and their importance in drug discovery, their future, seemingly is being threatened by complacency concerning their
conservation. Moreover, because of adverse side effects of many synthetic drugs, they are withdrawn years after their introduction into the market. It is thus the demand of the time to develop new drugs as many new diseases are continuously emerging and causative agents for many old diseases are becoming drug resistant. As different anatomical parts of the plants like root, leaves, flowers etc, may produce different set of metabolites, proper botanical knowledge of the plant is crucial for the correct taxonomical determination of the identified bioactive plants.

1.2. Euphorbiaceae family

Euphorbiaceae, the spurge family, is one of the largest families of flowering plants with over 300 genera and around 8000 species. The family is very much diversified, comprising of almost all types of plants that range from large woody trees through climbing lianas to simple weeds that grow prostrate to the ground. Members of the family have a world wide distribution comprising both old world as well as new world plants, with some of the members yet remaining to be identified. Several members of the family are found to be rainforest herbs and trees while others are found to be surviving the hot and dry desert conditions of tropical climate. Euphorbiaceae is a complex family having a wide research potential and the classification of the family has been difficult because of their complexity in habitat range and morphological and genetical variability (Mwine et al., 2011). Based on the phylogenetic structures such as pollen morphology and anatomy, Webster in 1975, divided the family into five subfamilies which are, Acalyphoideae, Crotonoideae, Euphorbioideae, Phyllanthoideae and Oldfieldoiideae. A per the new classification, the family Euphorbiaceae comprises of five subfamilies, 49 tribes, 317 genera and about 8000 species (Webster, 1994), thus making it one of the biggest plant families which probably finds the highest position in terms of species richness in many habitats. Similar to the complexity in classification, the ethno medicine of Euphorbiaceae is also diversified. This diversity, according to Seigler (1994), is
because of the presence of a wide range of unusual secondary metabolites which makes most of the members of the family poisonous. The family hosts ricin, one of the most poisonous substances of plant origin and is a protein found in *Ricinus communis*, whereas other species from the family like *Jatropha curcas* L. is reported to be comparatively poisonous. However, some members are reported to be the sources of useful substances. Many Euphorbiaceae have been used as popular traditional medicinal herbs since time immemorial. The genus *Euphorbia* as well as the family Euphorbiaceae has been named in honour of Euphorbus, a Greek physician to King Juba II of Mauritania. The physician was believed to use the latex of *Euphorbia resinifera* for curing ailments of the King, such as swollen belly (Mwine et al., 2011). As documented in the Indian traditional medicinal system, Ayurveda, since as early as 2 BC, many a members of Euphorbiaceae such as *Croton oblongifolius* Roxb. and *Croton tiglium* Wild have been used in the treatment of diseases like sprains, snake bites, liver ailments and also as purgative for the first as well as insanity, asthma, tumors, convulsions, rheumatism for the latter (Kapoor, 1989). Several researches have shown the potential role of many Euphorbiaceae as medicinal plants with many extracts being isolated as well as patented as modern drugs, of which some are registered drugs, available as such in the market. A very good example is Euphorbium (resiniferatoxin), isolated from latex of *Euphorbia resinifera* (Appendino et al., 1997) and is marketed as ‘Complexe Lehning euphorbium N 88’. It finds its application as a nasal spray or compositum against viral infection, rhinitis of various origins, chronic nasal discharge, dry and inflamed nasal membranes, sinusitis, and symptoms of flu.

Different plant families showing different medicinal properties may have their own good reasons for possessing such properties. In case of members belonging to Euphorbiaceae family, it may be due to their wide distribution in different habitats of the world which is being supported by their adaptations for survival, such as CAM pathway and succulence. The exposure of different members to widely varying habitats predisposes them to inevitably high mutation loads as well as a large range of environmental stimuli which necessitates in them
the development of defensive secondary metabolites of wide battery range. These
issues may explain why the family is widely pharmaceutical (Mwine et al., 201).

1.3. **Croton genus**

*Croton* is an extensive plant genus belonging to the family Euphorbiaceae. It was established by Carolus Linnaeus in 1737 (http://en.wikipedia.org/wiki/Croton_genus) and is one of the largest genera of flowering plants consisting of about 1200 to 1300 species of herbs, shrubs, trees and occasionally lianas which are of ecological prominence and important elements of secondary vegetation in the tropics as well as subtropics worldwide (Webster, 1993; Govaerts et al., 2000). The genus *Croton* is a member of the subfamily Crotonoideae, which as one of its characteristics; possess mostly lactiferous taxa bearing pollen of unusual (crotonoid) exine pattern. The supratectal elements are triangular and attached to a network of muri with short columellae (Nowicke, 1994). There has been a horticultural confusion with *Codiaeum*, which is a small and distantly related Malaysian genus belonging to the family Euphorbiaceae, whose common name "Croton" is being referred to the world wide cultivated ornamental varieties of *Codiaeum variegatum* (L). A. Juss. In the field *Croton* is usually readily recognizable by a suite of characters that includes conspicuous stellate or scale like trichones, narrow or condensed inflorescence of unisexual flowers, watery to coloured sap, frequent petiolar glands, senescent leaves that turn orange before dehiscing (De vries, 1989). The common names for the genus are russoil and croton. The genus name come from the Greek word "kroton" which means ticks, because of the seeds resemblance to ticks (http://en.wikipedia.org/wiki/Croton_genus).

1.3.1. **Croton distribution**

The genus *Croton* is widely distributed in tropical and subtropical regions of both the hemispheres (zspdelhi.wordpress.com/2008/06/27/the-ethnomedicinal-use-of-Croton/). Almost any habitat in tropics such as deserts, cloud forests, salt-
water beaches and even seasonally flooded forests is likely to yield one or more *Croton* species, though the most typical being the semiarid habitats. In the West Indies, Cuba has 51 species of *Croton*, of which 33 are endemic, covering 14 sections, as well as seven species of the closely related Moa *Croton* and the monotypic Cuba *Croton*. Nearly as diverse is Hispaniola having 45 species in 12 sections. Even the Southern U.S is surprisingly diversified in terms of distribution of *Croton*, having 42 species in 14 sections. Brazil is having the largest country count for *Croton* distribution, with 356 species in 26 sections, of which four states of southeastern Brazil having 172 species in 21 sections is the most species rich area for the genus in the world (www.botany.wisc.edu/berry/projects/crotonFB/Project background.htm. The Genus *Croton* (Euphorbiaceae). The following figure shows the hot spots of Croton distribution.

![Distribution and hotspots of Croton](image)

Figure 1.1. Figure showing distribution and hotspots of Croton (Berry et al., 2005).
1.3.2. *Croton* nomenclature

The 19th century classification of *Croton* by Muller (1866, 1873) was a highly artificial one, so Webster (1993) set out to revise the genus and divided it into 40 sections. For now Webster's sections are the best available framework of hypothesis for future phylogenetic studies. The systematic position up to the genus is as follows (*plants.usda.gov/java/profile?symbol=CRLO5*

Kingdom – Plantae
Subkingdom – Tracheobionta
Superdivision – Spermatophyta
Division – Magnoliophyta
Class – Magnoliopsida
Subclass – Rosidae
Order – Euphorbiales
Family – Euphorbiaceae
Genus - *Croton*

1.3.3. Species of *Croton*

The “giant genus” *Croton*, have about 1223 species accepted in the World Checklist and Bibliography of Euphorbiaceae (Govaerts et al., 2000). But others have put the number as 1797 starting with *Croton abaitensis* (1st species) and ending in *Croton zeylanicus* (1797th species). All the species under *Croton* are herbs, shrubs, trees and occasionally lianas (climbers) which are of ecological prominence and important elements of secondary vegetation in the tropics as well as subtropics worldwide. More than 30 species of *Croton* have been reported so far from India, of which only six species, namely *Croton bonplandianus* Bail., *Croton caudatus* Geisel., *Croton chlorocalyx* Linn., *Croton joufra* Roxb., *Croton roxburghii* Balakr. and *Croton tiglium* Linn have been reported to be used in ethnomedicine. The reported species are used in the treatment of various diseases, disorders and ailments like antifertility, fever, gastric disorders, insanity, jaundice, liver complaints, malaria, boils, bowel complaints, cold and coughs, constipation,
cuts and wounds, chicken pox, cholera, diarrhoea, dysentery, eye diseases, spasmyolytic agent, snake bite, epilepsy, rheumatism, ringworms, scurvy, sprains, etc. Recently the powdered roots of *Croton roxburghii* Balakr (known as Hongkai in Arunachal Pradesh), has been reported to be used in the treatment of cancer by the Khamti tribe of Arunachal Pradesh. Also the use of *Croton caudatus* Geisel in the treatment of cancer in the Saikot area of Manipur has been recently reported (zspdelhi.wordpress.com/2008/06/27/the-ethnomedicinal-use-of-Croton/).

**Croton caudatus** Geisel

**Vernacular names:** The plant is known by different names in different dialects or local languages in India, namely Ghahe-lewa in Assamese, Sawaka in Garo, Kum-kumarong in Karbi, Soh-lambrang in Khasi and Matau in Lusai. It is also known by the names of Sonaphula, Tilaker-rik in other Indian dialects. In Jiribum subdivision of Manipur the plant is known by the Manipuri names Yong Khulllokpi and Khagi laikoi. In Saikot area of Churachandpur district of Manipur the plant is known as Ranlung Damdawi or Chawilien Damdawi in Hmar language. In Philippines the plant is known as Alampai, in Malaysia as Tapasan Komudi and in China the plant is probably known as luan ye ba dou (zspdelhi.wordpress.com/2008/06/27/the-ethnomedicinal-use-of-Croton/).

**Distribution:** *Croton caudatus* is distributed from the Eastern Himalayas to Sri Lanka, from Southeast Asia and West Malaysia to the Philippines and Sulawesi (www.globinmed.com/index.php?...croton-caudatus-geiseler...c). In India the plant is reported from the north eastern states like Assam, Meghalaya, Manipur, Arunachal Pradesh and Sikkim. It is also reported from Western Ghats and Orissa (zspdelhi.wordpress.com/2008/06/27/the-ethnomedicinal-use-of-croton).
**Taxonomic hierarchy:**

Kingdom – Plantae

Subkingdom – Tracheobionta

Superdivision – Spermatophyta

Division – Magnoliophyta

Class – Magnoliopsida

Subclass – Rosidae

Order – Euphorbiales

Family – Euphorbiaceae

Subfamily - Crotonoideae

Genus – Croton

Species - caudatus

**Scientific name:** *Croton caudatus* Geisel.

**Description:** *Croton caudatus* Geisel is a straggling shrub bearing leaves which are extremely variable in shape, the smaller ones being ovate-cordate and 2.5 to 7.5 centimeters long and larger ones, orbicular-cordate and 10-18 cm long. The margins of the leaves are coarsely toothed and often have a gland at the sinus or else in the teeth. The racemes are very long, slender, 10-18 cm long solitary and terminal in position. The staminate flowers are hairy, having sepals and petals of equal length. In pistillate flowers, the sepals are ovate or oblong and the petals are very minute and long, ciliated. The fruit (capsule), is woody nearly spherical or broadly oblong, 2-2.5 cm long, with six slender ridges, densely yellow-brown stellate-hispid. The seeds are unusually variable in form mostly being dorsally compressed and slightly rugose. Flowering may occur during the month of May to August and fruiting during July to October. ([zspdelhi.wordpress.com/2008/06/27/the-ethnomedicinal-use-of-croton](http://zspdelhi.wordpress.com/2008/06/27/the-ethnomedicinal-use-of-croton)).

**Ethnomedicinal information:** The plant finds its use in traditional folk medicine mainly in South East Asia. It has also been an important part of Dai medicine in
China. In Malaysia the infusion of the boiled root of the plant is used in the treatment of weak body and in avoiding several diseases. The application of leaves and root of the plant as poultice in sprains, in malaria and as diuretic in the Western Ghats region of India has been reported. Decoction of the root is administered for constipation as it causes purging. The plant also finds utility in the treatment of cold. The young leaf buds are powdered along with the leaves of *Caesalpinia sappan* in Lakhimpur and used in the treatment related to liver ailments. The plant is known as Bonmahudi in the Chandrapur area of Kamrup, Assam and the barks and roots of the plant are used as pain relieving and antidysenteric substances. In Tirap District of Arunachal Pradesh, the leaves are used in liver ailments and the poultice in treating trauma and injury. The decoction of the leaves and roots are used in the treatment of cold and cough in the Subansiri District of Arunachal Pradesh. The decoction of the roots is used in treating malaria in the Balphakram Wild Life Sanctuary area of Meghalaya (Garo Hills). In the Totopara and Jalpaiguri areas of West Bengal, the leaves of the plant are used in treating sprains. Meitei community from Jiribam sub-division of Manipur uses the plant for the treatment of ringworms. It is also used in the treatment of wounds in cattle. However, in the Saikot area of Manipur, the reports of the use of the plant leaves in treating cancer, is a new record in the world of ethnobotany as well as ethnomedicine. (zspdelhi.wordpress.com/2008/06/27/the-ethnomedicinal-use-of-croton).
Figure 1.2. Photographs of *Croton caudatus* Geisel. (A): Plant in the natural habitat. (B): Plant showing dehiscing leaves (orange colour). (C): Plant with the fruit. (D): Herbarium of the plant.