Chapter 2

Review of Literature
The value of plants used in traditional medicine has great importance on bioactivity guided natural product and drug discovery research. With rapid industrialization and loss of ethnic culture, many useful plants may disappear. Though there is abundance of information stored in many scientific literatures, most of them have not been compiled in a useful form. Survey of literature and other related data based on the report by Farnsworth et al. (1985) and Fabricant and Farnsworth (2001), a total of 122 compounds were identified of which 80% have same or related ethnomedicinal use. With vast diversity of plants, it is believed that abundance of drugs still remained to be discovered. Ethnomedicinal approach to drug discovery is highly diversified and involves observations descriptions and experimental investigation of the indigenous drug following biological screening. Phytochemical screening approaches, i.e., for the presence of alkaloid, terpenoid, steroid, etc. have proved fruitful in identifying the plant, for further phytochemical analysis leading to drug discovery, although these results sometimes yield false-positive and false-negative inferences that makes the results difficult to assess and interpret. It has been observed that 87% of all categorized human diseases can now be cured by drugs of natural product origin. The analysis of data on the origin and
development of drugs from 1981 to 2002 showed that 28% of all new chemical entities launched in the market were natural products or natural product derived drugs (Newman et al., 2002). The combined percentage of all new chemical entities (52%) showed that natural products are good source of new drugs and also good lead compounds suitable for further modification (Chin et al., 2006). Various natural products isolated in between 2000 to 2005 from plants and microorganisms are shown below.
Apomorphine hydrochloride is a short acting dopamine D1 and D2 receptor agonist, is a potent dopamine receptor agonist used to treat Parkinson’s disease, a chronic neurodegenerative disease (Deleu et al., 2004). Tiotropicum bromide, a natural product isolated from Atropa belladonna (Solanaceae) has been approved by United States Food and Drug Administration (FDA) is used for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) (Koumis and Samuel, 2005). Nitisinone is a derivative of leptospermone, a new class of herbicide isolated from Callistemon citrinus and used in treatment of liver and kidney disease. Galantamine hydrobromide, an Amaryllidaceae alkaloid obtained Galanthus nivalis used in the treatment of neurological disorders. Arteether, an antimalarial agent developed from Artemisia annua (Asteraceae) used in traditional Chinese medicine as remedy for treatment of fever (Howes et al., 2003; Heinrich and Teoh, 2004).

The cephalotaxus alkaloid, Homoharringtonine isolated from Cephalotaxus harringtonia is an inhibitor of protein synthesis and is reported to have against hematologic malignancies (Kantarjian et al., 2001). Ingenol 3-O-angelate is an analog of the polyhydroxy diterpenoid Ingenol from Euphorbia peplus is used as a chemotherapeutic agent for skin cancer and exhibits its action through
activation of protein kinase C (Kedei et al., 2004). Phenoxydiosiol, an isoflavone isolated from Glycine max is used in therapy of cervical, ovarian, prostate, renal and vaginal cancers and induced apoptosis through inhibition of anti-apoptotic proteins including XIAP and FLIP (Kamsteeg et al., 2003). Protopanaxadiol is a derivative of a triterpene aglycone of several saponin from Panax ginseng exhibits apoptotic effects on cancer cells (Shibata et al., 1963; Jia et al., 2004).

The use of plant extracts in treatment of diseases is not new. Various plants have been used for centuries in the treatment of various infectious diseases. Plants with anti-microbial activity are also known to be numerous. Micro-organisms being ubiquitous in the environment and infection due to microbes have become more frequent (Walsh and Groll, 1999; Fleming et al., 2002). Fungal infections are usually opportunistic infections and have become a common cause of morbidity and mortality (Garbino et al., 2001) and incidence of such infections have increased drastically (Rubin et al., 1981; Winston et al., 1995; Fishman and Rubin, 1998). The search for novel anti-microbial drug has been influenced by ethnobotanical information and such studies have been successful with a high degree of correlation between traditional and laboratory analysis (McCutcheon et al., 1994; Bergeron et al., 1996; Jones et al., 2000). More importantly, in most of the studies, the alcoholic
extracts have been found to possess high degree of antifungal and other anti-microbial property (Ali-Shateyeh and Abu Ghdeib, 1999). Webster et al. (2008) studied aqueous extracts of 14 different plants against *Trichophyton tonsurans*, *T. rubrum*, *T. mentagrophytes*, *Microsporum canis*, *Epidermophyton floccosum*, *Aspergillus fumigatus*, *Aspergillus flavus*, *Fusarium solani*, *Rhizopus* spp., etc. Of the 14 plants, *Fragaria virginiana* Duchesne, *Epilobium angustifolium* L. and *Potentilla simplex* Michx showed strong antifungal activity (Webster et al., 2008). The anti-microbial potentiality of many traditional plants has been increasing.

The *in vitro* and clinical efficacies of several plants have been reported. *Melaleuca alternifolia* has been used by the Australian Aborigines in their traditional medicine as a fungicidal agent against fungal pathogen (Hammer et al., 2003). In addition to this, *Acorus calamus* has also been reported to have potential fungistatic activity (Thirach et al., 2003). Plants like *F. virigiana*, *E. angustifolium* and *P. simplex* have been reported to have strong anti-microbial activity (Jones et al., 2000). Romano et al. (2005) studied bergamot oil to be active against clinical isolates of *Candida* suggesting its potential role in topical treatment of *Candida* infections.

With the advancement of medicine in last few decades, there is no effective drug to stimulate liver function, protection and regeneration
Large numbers of herbal medicinal preparations have been reported in ethnobotany that can help in curing liver ailments and act as a hepatoprotective agent (Chaterjee, 2000). *Momordica dioica* Roxb. is being used in traditional medicine in curing jaundice and urinary calculi. The ethanolic extract of the leaves have been reported to have significant hepatoprotective activity (Jain et al., 2008). However, there are few data available on hepatoprotective activity of plant extracts.

The *in silico* techniques have been used in drug discovery. The identification of a proper lead compound for a given molecular target is a critical step in the process of drug discovery. Analysis of a compound to be probable drug is the first step in this regard. In modern computational chemistry, defined features of one or more molecule with the same biological activity are used. A pharmacophore was first defined by Paul Ehrlich in 1909 as “a molecular framework that carries (phoros) the essential feature responsible for a drug’s (pharmacon’s) biological activity”. In 1977, this definition was updated by Peter Gund to a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule’s drug activity. In IUPAC classification, pharmacophore is an ensemble of steric and electronic feature that is necessary to ensure the optimal
supramolecular interactions with a specific biological target and to trigger or inhibit its biological function. The features for a compound to be a pharmacophore is that the compound has to be either hydrophobic, aromatic, hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), cation or an anion.

Plants used in traditional medicine have been contributing significantly in drug discovery. The main objective of every ethnobotanical investigation lies in finding out the bioactive component of the plant alleged for its bioactivity and here starts natural product and drug discovery researches. *Pajanelia longifolia* (Willd.) K. Schuman is an ethnomedicinal plants reported from Southern Assam (Dutta Choudhury, 1999; Choudhury, 2007). The bark of this plants is extensively used by the Reang and Chorei tribes against jaundice. The crude extract of the 2-3 young leaves are applied against skin infection and nail decay (Dutta Choudhury, 1999; Choudhury, 2007). Only one active principle Pajanalin was reported from this plant till date (Wealth of India Raw Material Series).