GENERAL INTRODUCTION AND OBJECTIVES

The study of medicinal plants always had an important role in the development of modern medicine. Use of medicinal plants and the products obtained from them is thought to have originated from mankind’s curiosity about odor, taste and cures for diseases. Traditional and folklore knowledge about medicines, which was passed on from generation to generation, is rich in household remedies and community practice. Fossil records date human use of plants as medicines at least to the Middle Paleolithic age some 60,000 years ago (Solecki 1975). From that point, medicinal plants have been incorporated in traditional medical systems of different countries of the world, as a means of therapy. The practice of traditional medicines is widespread in China, India, Egypt, South Africa, Greek, Italy, Japan, Pakistan, Sri Lanka and Thailand. The traditional medicine systems of China and India are still prevalent. Traditional Chinese Medicine, also known as TCM, includes a range of traditional medicine practices originating in China. The use of ginseng, mushroom, wolfberry, dang gui, astragalus, atractylodes, bupleurum, cinnamon, coptis chinensis, ginger, licorice, ephedra, rhubarb, salvia etc., is known well over two thousand years old in Chinese medicine. Traditional medicine system in India mainly refers to three disciplines i.e. Ayurveda, Siddha and Unani, in which use of several plant species has been mentioned to treat different ailments. Recent studies have revealed the presence of around 20,000 medicinal plant species in India (Dev 1997). Out of that only 500 plants with medicinal use are mentioned in ancient texts and around 800 plants have been/are being used in indigenous systems of medicine for curing different diseases (Kamboj 2000).

For quite a long time, the only way to use plant medicines was either direct application or the use of crude plant extracts. But with the development of chemistry at the beginning of this century, extraction and fractionation techniques improved significantly. It became possible to isolate and identify many of the active chemicals from plants which not only found use directly as therapeutic agents but also provided leads for synthesis of new drugs. These molecules also are starting materials for the synthesis of drugs or as models.
for pharmacologically active compounds (Mukherjee 2003) In the last century, roughly 121 pharmaceutical products were formulated based on the traditional knowledge obtained from various sources (Anesini and Perez 1993). Plant based drugs provide outstanding contribution to modern therapeutics; for example: reserpine (1) isolated from the root of Indian plant *Rauwolfia serpentina* in 1953, was a revolutionary event in the treatment of hypertension and lowering of blood pressure. During 1950-1970 approximately 100 plant based new drugs were introduced in the USA drug market including deserpidine (2), vinblastine (3), vincristine (4), compactin (5) and lovastatin (6) etc., which are used even today and represent successes in both medical treatment and in pharmaceutical business fortunes.

From 1971 to 1995 plant based new drugs such as etoposide (7), teniposide (8), paciltaxel (9), guggulsterone (10), nabilone (11), artemisinin (12), ginkgolides (13), toptecan (14), irinotecan (15) and lentinan (16), appeared all over the world. Podophyllotoxin (17), a constituent of *Podophyllum emodi* is currently being used against testicular, small cell lung cancer and lymphomas.
In spite of successful discovery of drugs from plants and development programs based on natural products, the pharmaceutical industry, in particular the large pharmaceutical companies de-emphasized natural product discovery research in the 1990s and early 2000s.

By 1990, about 80% of drugs were either natural products or analogs inspired by them. Antibiotics [ penicillin (18), tetracycline (19), erythromycin (20)], antiparasitics [ avermectin (21)], antimalarials [artemisinin (22)], lipid control agents [lovastatin (6)].
immunosuppressants for organ transplants \[\text{cyclosporine (23)}, \text{rapamycins (24)}\] and anticancer drugs \[\text{doxorubicin (25)}\] isolated from medicinal plants revolutionized medicine.
The expansion of synthetic medicinal chemistry in the 1990s caused the proportion of new drugs based on natural products to drop to ~50% (Harvey 2008).

A total of 13 natural products (NP) and NP-derived drugs were approved for marketing worldwide from 2005 to 2007, with 5 being classified as NPs, 6 semi-synthetic NPs and 2 NP-derived drugs. In addition, retapamulin (26), trabectedin (27) and ixabepilone (28) are the first members of new human drug classes. To further support the importance of NPs in drug discovery, it should be noted that 6 of 27 small molecule drug launches in 2005 (22%), 2 of 21 in 2006 (9%) and 5 of 21 (24%) in 2007 were NPs or derived from NPs, and the numbers are greater if we consider drugs inspired from other naturally occurring molecules such as steroids, nucleosides, prostaglandins, hormones and vitamins. (Butler 2008). More than 100 natural product–based drugs are in clinical studies. In the last decade, marketed drugs derived from natural products still account for significant revenues for many of the major pharmaceutical companies. For examples drugs like Lipitor (29), Zocor (30) and Pravachol (31), statin class of compounds derived from the natural products, continue to generate multi-billion dollar revenues for pharmaceutical companies.
With such a successful record, it might be expected that the identification of new metabolites from medicinal plants would be the core of pharmaceutical discovery efforts. The future of drug discovery in the natural products is more holistic, personalized and involves wise use of ancient and modern therapeutic skills in complementary manner so that maximum benefits can be given to patients and the community (Patwardhan 1992). Now in 21st century, age of the blockbuster drugs seems to be over or in at least in its last days. The data from a study done by DiMasi and Paquette of Tufts University, suggest that entry barriers have fallen over time for new drug introductions. The increased competitiveness of the pharmaceutical market place was likely fueled by changes over time on both the supply and demand sides. The pharmaceutical industry has not been as innovative as it claims to be and the regulatory processes are adding more risk and years for the pharmaceutical companies and it is predicted that worst is yet to come. Today, most of the big pharmaceutical companies spend more on marketing than on research and development. Drug companies these days are focusing their research either on new ways to interact the drug with known receptors or seek out new receptors. Beside this, a whole range of chronic and difficult-to-treat diseases like cancer, cardiovascular disease, diabetes, rheumatism and AIDS, side effects of modern drugs, problems with drug-resistant microorganisms and emerging new diseases have stimulated the interest of researchers in plants as a significant source of new medicines. As a number of synthetic drugs have adverse and unacceptable side effects, the pharmaceutical companies have now changed their approaches and are looking for traditional knowledge and ethnopharmacology for drug discovery. Because traditional knowledge and experiential database can still have potential to provide new functional leads in short time, spending less money and without toxicity - the three main hurdles in the drug development (Patwardhan et al. 2004) The main emphasis of research now is for such therapeutic agents which work according to body’s mechanism and have least side effects. There have been impressive successes and increase in the consumption of herbal drugs, herbal extracts/formulations, and most notably pure isolated molecule from herbs /medicinal plants because consumers gave preference for natural therapies over modern medicine. Today consumers are very much concerned regarding undesirable side effects of modern medicines and they believe that
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herbal drugs are free from side effects, since millions of people all over the world have been using herbal medicines for thousands of years and the belief that herbal medicines might be of effective benefit in the treatment of certain diseases where conventional therapies and medicines have proven to be inadequate.

The global market for herbal medicines currently stands at over $60 billion annually. Due to the contribution of numerous significant factors discussed above, the market of herbal medicines has grown at an express rate worldwide (Sharma et al. 2008). India is one of the 12 mega-diversity hot-spot regions of the world, other countries being Brazil, Colombia, China, South Africa, Mexico, Venezuela, Indonesia, Ecuador, Peru, USA and Bolivia. Almost, 70% modern medicines in India are derived from natural products. Two of the largest users of medicinal plants are China and India. Traditional Chinese Medicine (TCM) uses over 5000 plant species; India uses about 7000. According to Export Import Bank, the international market for medicinal plant related trade is to the tune of US$ 60 billion having a growth rate of 7% per annum. China's share in world herbal market is US$ 6 billion while India's share is only US$1 billion (Rawat 2002) which is very small for countries like India as India has one of the richest plants medical traditions in the world. There are estimated to be around 25,000 effective plant-based formulations, used in folk medicine and known to rural communities in India. There are over 1.5 million practitioners of traditional medicinal system using medicinal plants in preventive, promotional and curative applications. It is estimated that there are over 7800 medicinal drug-manufacturing units in India which consume about 2000 tones of herbs annually. Despite such rich herbal wealth in national market, the total turnover of India in International herbal market is very less. According to Mehrotra (2003), the reason behind this low share is lack of quality control and standardization measures. Hence, standardization and quality control of the herbal drug on the basis of botanical, physical, Phytochemical and biological parameters on the modern line is highly essential.

Standardization of herbal drugs/formulation arouse out of the need to create a uniform product for clinical trials, which is based on identifying and quantifying an extract either on the basis of one or more characteristic chemical marker compound or on the basis of active principle of the bioactive extracts/drug/formulation. Standardized herbals /natural products represent a trend towards higher technological refinement. They provide a more
consistent, stronger and more effective product backed by chemical analysis to confirm the presence and ratio quantity of one or a number of characteristic plant constituents. This increases consumer confidence and that this is ultimately good for greater acceptance of herbs by the medical establishment and the mainstream. As we know that today pharmaceutical companies are rapidly entering the herbal market because the potential of herbal market is huge and growing incrementally. But herbs unlike chemical drugs, themselves are not patentable. However, a standardized product used for research/alignments is patentable. Hence there is a need for standardization of active herbal extracts or herbal formulation(s). Every Herbal Formulation must be standardized as per WHO guidelines (Chaudhri 1996). World Health Organization currently recommends and encourages traditional herbal remedies in natural health care programs because these drugs are easily available at low cost and are comparatively safe. Peoples’ faith in such remedies is reflected by a whooping turnover of 450 Crore rupees annually in herbal market besides a healthy 11% annual growth rate and the increasing export potential has attracted several large and medium scale pharmaceutical industries and even multinationals to jump on to the bandwagon (Handa and Kapoor 1995). Internationally several pharmacopoeias such as Chinese Herbal Pharmacopoeia, United States Herbal Pharmacopoeia, British Herbal Pharmacopoeia, British Herbal Compendium, Japanese Standards for Herbal Medicine have provided monographs stating parameter and standard of many herbs and some product made out of these herbs. These Pharmacopeias lay down monograph for herbs and herbal products to maintain their quality in their respective nations. Government of India too has brought out Ayurvedic Pharmacopoeia India, which recommends basic quality parameters for eighty common Ayurvedic herbal drugs. (Verma and Singh 2008)

Several researchers are currently working on bioassay-guided extraction, fractionation and isolation of pure chemical constituents from the medicinal plants / herbs that showed high biological activity during screening. Therefore, these scientific investigations may be utilized to develop drugs for many diseases. Plants are the only sources which can provide either molecules or leads for the cure of different alignments/diseases. For the benefit of mankind to target various incurable disease exploration of the plant is
necessary. At present about 80% of world’s populations relies predominantly on plants and plant extracts for health care. About 25% of the more important prescriptions are based on plant derived drugs. Among these medicinal plants, *Asparagus racemosus*, *Tanacetum gracile* and *Podophyllum hexandrum* are well reputed due to their use in traditional system of medicine and source of modern drugs.

Modern approaches to understand the action of plant constituent all the time rely on careful structural characterization that is predominantly done by UV, IR, NMR and mass spectroscopy. Therefore, natural products chemistry, especially phytochemistry, has proven to be the single most successful approach in finding new medicines.

**Nitrogen Heterocycle – General Introduction**

Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structures. Numerous examples occur, among the carbohydrates, essential amino acid, Vitamins, alkaloids, glycosides, or antibiotics. The presence of heterocyclic structures in such a diverse type of compounds is strongly indicative of the profound effects, such structure can exert on physiological activity, and recognition of this is reflected abundantly in efforts to find useful synthetic drugs. Example include researches leading to a wide variety of modern drugs such as chloradiazepoxide (32) [tranquillizer], guanethidine (33) [antihypertensive], dapsone (34) [laprostatic], cyclophosphamide (35) and thiotepa (36) [antineoplastic], hydrochlorothiazide (37) [diuretic and antihypertensive], imipramine (38) [antidepresent] and many others (Remington 2000).
An inspection of the structure of top selling drugs in 2007 reveals that 8 of top 10 and 71 of 100 drugs contain heterocycles. Heterocycles have dominated the medicinal chemistry from the beginning (Quin and Tyrell. 2009).

**Nitrogen heterocycles** contain nitrogen atom/atoms along with carbon atoms in the ring, are key building blocks used to develop compounds of biological or medicinal interest. A vast number of nitrogen-containing heterocyclic building blocks have applications in pharmaceutical research, agricultural science, and drug discovery. The delicious and appetizing flavor of many every day foods are heterocycles. Many natural drugs such as quinine (40), emetine (41), morphine (42), atropine(43), papaverine(44), and theophylline (45) are N- heterocycles. They also constitute a large number of synthetic dyes and drugs.

Almost all the compounds we know as synthetic drugs such as atorvastatin (46) [cholesterol-reducing], celecoxib (47) [anti-inflammatory], cimetidine (48) [antiulcerative], tazobactam (49) [β-lactamase inhibitory], fluconazole (50) [antifungal], losartan (51), chlorpromazine (52), and methotrexate (53) [antihypertensive] also come under same class.
Some dyes [e.g. mauveine A (54)], luminophores, [e.g. acridine orange (55)], pesticides [e.g. diazinon (56)] and herbicides [e.g. paraquat (57)] also contains N-heterocyclic ring.

N-heterocyclic systems occur in a wide variety of natural and synthetic compounds and are essential to life in various ways. Keeping in the view, importance of these compounds, the synthesis of Chalcones and Pyrido[1,2a] pyrimidin-2-one, all being a class of N-heterocycles been undertaken in present study.
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Objectives of the present study

Keeping in the view the importance of bioactive molecules as mentioned above, the research work was envisaged to carry out in two parts as given hereunder –

**Part A**: This deals with the phytochemical investigation (extraction, fractionation isolation and characterization of pure molecules) and standardization of the extracts/fractionations on the basis of isolated molecules from some selected Indian medicinal plants and constitutes three chapters (Chapter 1-3) of the dissertation. The plants selected for these studies are -

2. *Tanacetum gracile* Hook. f & T.

**Part B**: This deals with the synthetic studies towards biologically important N-heterocycles and constitutes the two chapters (Chapter 4-5) of the dissertation.

5. Pyrido [1, 2a]-pyrimidin-2-one derivatives and their precursor N-(1,3-dioxobutyl)-2-aminopyrimidine.

Each chapter describes introduction and review of literature followed by materials and methods, result and discussion, conclusion and experimental data. References are given at the end of the chapter.

**Chapter-1** deals with the chemical investigation of roots of *Asparagus racemosus* Wild. which describes the isolation and characterization of new and known compounds, assessment of immunomodulatory activities and development of method for determination of secondary metabolites in the plant.

**Chapter-2** deals with the phytochemical investigation of Aerial part of *Tanacetum gracile* Hook. f & T which involves the extraction, isolation and characterization of compounds, assessment of immunomodulatory activities, GC-MS determination of essential oils constituents, development of HPLC method for the determination of flavanoids.
Chapter-3 deals with the phytochemical investigation of *Podophyllum hexandrum* Royle which includes the isolation and characterization of compounds and assessment of radioprotective activity, development of HPLC method for determination of lignans and phenolics in plant.

Chapter 4 describes syntheses of new hetryl chalcones, and assessment of their antioxidant, anti-inflammatory, antimicrobial and anticancer activities.

Chapter 5 deals with synthesis of new derivatives of pyrido[1,2-α]pyrimidin-2-ones and N-(1,3-dioxobutyl)-2-aminopyrimidine/picoline and evaluation of antiinflammatory activity.
REFERENCES


