INTRODUCTION AND OBJECTIVES

"You can resist an invading army, You can not resist an idea whose time has come"

– Victor Hugo –
I. INTRODUCTION AND OBJECTIVES:

Plants have been used as therapeutic regimen for thousands of years, based on experience and folk remedies and continue to draw wide attention for their role in case of mild and chronic diseases. In recent times, the interest in the use of herbal products and the focus on plant research has grown dramatically in the western world as well as developed countries (Loya et al., 2009; Mythilypriya, 2007; Sparreboom et al., 2004; Vaidya, 1997). Medicinal herbs as potential source of therapeutic aid has attained a significant role today in health system all over the world, not only in the diseased condition but also as potential material for maintaining proper health.

The size of the worldwide market of herbal medicines is estimated to be around US $80 billion to US $100 billion and this market is expected to reach US $2500 billion in near future (Mathur, 2003; Agrawal et al., 2006). In the west, the demand for herbal drugs has reached a new high in recent years. Since 1999, the global market for herbal supplements exceeded US $15 billion, with a US $7 billion market in Europe, US $2.4 billion in Japan, US $2.7 in the rest of Asia and US $3 billion in North America (Wakdikar, 2004). The results of a nationwide survey in USA indicated a marked increase in the number of individuals using alternative therapies between 1990 and 1997 estimating total out-of-pocket expenditures for alternative therapies at $27 billion (Eisenberg et al., 1998). According to a recent estimate in a study, 70-80% of the world population especially in developing countries relies on traditional medicine, mostly plant drugs for their primary healthcare needs (Agrawal et al., 2006). About one third of the adults in developed countries and more than 60% Asians use herb as an alternative medicines (Zhou, 2007).

As the use of herbal medicines is steadily growing, public, academic and government interest in traditional medicines is growing exponentially due to the increased incidence of the adverse drug reactions and economic burden of the modern system of medicine (Charrois et al., 2007).
A major factor impeding the therapeutic utilization of medicinal plants is the lack of information on various herbal drug interactions.

Herbs have been used in clinical medicine for thousands of years, but it is only in recent times that we have been able to employ scientific methods to prove the efficacy of many of these herbs and to give us a better understanding of their mechanisms of actions. Except for the use of these plants for local health care needs, not much information has been available on their safety, mechanisms of interactions with allopathic and other alternative medications, consumption patterns and possibilities of various potential interactions in Indian populations as the use of alternative therapy is mostly not supervised by physicians or alternative therapy practitioners resulting in increased harm to patients, especially if they are using herbal and prescription medicines that have latent interactions. These interactions can go unnoticed until a patient is hurt or a serious life-threatening event has occurred. The caution was raised on the line that, despite the urgent need for information, very little is known about herbal drug interactions unfortunately as experimental data in this field is limited and case reports and case series are rare (Fugh-Berman, 2000; Fugh-Berman and Ernst 2001). Several reasons could be cited as responsible for the same including,

1. Research on herbal therapies is still not nearly as advanced as research on pharmaceutical drugs.

2. Herbal products are not studied or monitored for safety and potential interactions to the same extent as prescription drugs. Studies of prescription drugs rarely consider potential interactions with herbs.

3. Traditionally, herbal products have not been regulated for purity and potency. The ingredient of herbal products can vary greatly between manufacturers and even between batches from the same manufacturer (Cupp, 1999). Without a standard for purity and potency, the possibilities increase greatly for herb-drug or herb-herb interactions, or reactions to contaminants, like heavy metals (Fugh-Berman, 2000; But, 1994).
Besides posing risks of toxicity for patients, it is also difficult to verify reports on herbal drug adverse reactions due to numerous unknown variables.

4. Most healthcare practitioners do not have clinical experience combining herbs and drugs because there is so little research on the same and whatever information about such interactions available is usually collaged from several different sources like:
   – Anecdotal information, clinical experience and reports of potential interactions in the literature.
   – Reasonable likelihood of an interaction based on knowledge of how specific drugs and herbs work together.
   – *In vitro* (test tube) studies, particularly studies of liver cell metabolism.
   – Observational studies regarding the use of herbal therapies.
   – Pharmacokinetic studies that directly measured fluctuations in amount of drugs in the blood.

There is an ever-increasing need for detailed information in this area as the millions of people use herbal therapies along with prescription and non-prescription medications today (Zhou, 2007). Although considered natural, concurrent use of many of these herbal therapies herbs may mimic, magnify or oppose the effect of drugs and thus may raise the potential of interactions causing either potentially dangerous side effects and/or reduced benefits from the medications, contrary to the popular belief, that nature is always safe (Izzo, 2005; Hu et al., 2005; Izzo et al., 2002; Izzo and Ernst, 2001; Fugh-Berman, 2000; Blumenthal, 2000; Miller, 1998).

For the most part, the possibility of herbal drug interactions had been largely ignored during this revival of medicinal herb use. A strong impetus to look at the problem more closely came from the finding that grapefruit juice could impair drug metabolism and result in significant changes in the expected drug activity (Bailey et al., 1989). This discovery did not come to public observation until several years later, when the use of herbs had become even more widespread.
The discovery that grapefruit juice could alter drug metabolism was the serendipitous result of using the juice as part of a placebo preparation in a drug test conducted in Canada (Bailey et al., 1989).

In the study cited here, a calcium channel blocker drug felodipine (vasodilator, diuretic; used for hypertension) was evaluated for interactions with alcohol where alcohol did affect the way the drug functioned, resulting in more side effects, and mainly postural light-headedness due to hypotension. The plasma concentrations of the drug in the placebo group that had received grapefruit juice rather than alcohol were surprisingly high. The same researchers then performed a follow-up study (Bailey et al., 1991) using either grapefruit juice or orange juice; the grapefruit juice was found to increase the bioavailability of nifedipine, a calcium channel blocker, by an average of 284% (that is, there was nearly 3 times the amount in the blood of those who consumed grapefruit juice as those who consumed water). Orange juice had no such effect, indicating that it was a particular component of grapefruit juice that was responsible for this marked effect (Bailey et al., 1991). It was suggested in the same study, that the intentional combination of grapefruit juice and a lowered drug dose might yield a desired result of proper plasma levels of the drug with lower amounts ingested.

In the years that followed, numerous drugs were found to be responding the same way to grapefruit juice (Ameer and Weintraub, 1997), including antidepressants fluoxetine, trazodone (Dreier, 2004) and quinine (Hermans et al., 2003). The adverse effects were due to the greatly increased amount of drug in the bloodstream due to inhibited drug metabolism. The question that immediately surfaced in mind was, if an ordinary food like grapefruit could cause this response, why not herbs? Among the other issues of herb-food, interactions which incited thought process were these:

– It was recognized that certain foods interacted with a broad class of antidepressant drugs (Gardner et al., 1996) so, the question that surfaced in mind was: how safe the combination of the same with herbs?
It was noted that green vegetables could antagonize the effect of warfarin, the most commonly used blood thinner (Saw et al., 2007; Stout, 2006; Booth et al., 1999). So a fact to ponder was that herbs appear no different than green vegetables.

The drugs which have a more propensity to cause wider interactions are the ones that are indicated for the continuous long term use for chronic diseases. The herbal medicines are also mostly taken for long time. So combining them could turn out to be disastrous, especially on a chronic therapy (Boullata, 2005; Rafferty, 2001).

While the rationality of these questions was lingering in mind, we avidly noted the case reports on herb-drug interactions which were continuously surfacing in the literature at the same time (Engdal et al., 2009; Rommel et al., 2009; Nivitabishekam et al., 2009). In review of previous studies (Fugh-Berman, 2000; Fugh-Berman and Ernst, 2001) and a comprehensive review studies conducted by us (Patel and Gohil, 2008; Gohil and Patel, 2007), many such cases have been studied and validated using systematic algorithms. Herbs that had been widely popularized, such as St. John’s wort, ginkgo, and ginsengs were specifically cited as the most common herbs causing various interactions with drugs (Fugh-Berman 2000, Fugh-Berman and Ernst, 2001; Patel and Gohil, 2008; Gohil and Patel, 2007). Simultaneously many reports of such interactions with herbs like, Saw palmetto, green tea, ginger, garlic, danshen and cranberry juice were noted and validated (Patel and Gohil, 2008; Gohil and Patel, 2007). The reports also kept emerging in literature on various cases of herbal-drug interactions (Zhou and Lai, 2008; Nowack, 2008; Tovar, 2009; Gordon et al., 2009). The drugs of most concern for interactions with herbs were turned out to be mostly those that people took continuously such as blood thinners prescribed after a heart attack or stroke (Patel and Gohil, 2008; Saw et al., 2007; Stout, 2006) and antidepressants (Armstrong et al., 2000). Cases have been published reporting enhanced anticoagulation and bleeding when patients on long-term warfarin therapy also took cranberry juice (Suvarna et al., 2003; Grant, 2004; Rindone and Murphy, 2006), St. John’s wort (Yue and Jansson, 2001), birch (Joss and Leblond, 2000), danshen (Izzat, 1998; Tam et al., 1995), garlic
(Sunter, 1991; Rose et al., 1990), ginseng (Rosado, 2003; Janetzky and Morreale, 1997), Saw palmetto (Yue and Jansson, 2001; Cheema et al., 2001), ginkgo (Mathews, 1998; Fessenden et al., 2001), or green tea (Taylor and Wilt, 1999) simultaneously. Similarly, St. John wort, widely prescribed for various psychopathologic conditions involving depression and anxiety (Cupp, 1999) was reported for having pharmacodynamic interactions with various antidepressants (Lantz et al., 1999), namely paroxetine (Waksman et al., 2000), sertraline (Barbanel et al., 2000), nefazodone (Gordon, 1998), venlafaxine (Prost et al., 2000), clonazepam, midazolam (Tweddell and Boyle, 2009) and with antipsychotics like haloperidol (Khwaja et al., 1999).

While compiling all the data, it also came to our attention that the annual prescription of antidepressants has increased rapidly, since the approval of fluoxetine in the United States nearly 20 years ago; as the depression became a significant health problem today, projected to reach second place as leading contributor to the global burden of disease by the year 2020 (Harro, 2004).

However, despite the increasing number of new antidepressants introduced to the clinic, the quality of treatment still remains poor with these synthetic antidepressants. Although these treatments for depression are generally safe and effective, they are far from ideal. In addition to the need to administer the drugs for weeks or months to see clinical benefit, side effects are still a serious problem even with the newer medications. And most importantly, less than half of all patients with depression show full remission with optimized treatment, including trials on numerous medications with and without concurrent psychotherapy (Berton and Nestler, 2006). As a consequence, there have been a growing number of patients turning to alternative medicine treatments for a more effective cure (Nancy and Pang, 2008; Murray and Lopez, 1997).

Moreover, it is now becoming exceedingly apparent that available psychotherapeutics does not properly meet therapeutic demands of a vast majority of patients with mental health problems, and that herbal remedies remain to be the ultimate therapeutic hope for many such patients in the western world and elsewhere (Husain et al., 2007).
The vast majorities of currently available psychoactive drugs as herbal remedies seem to be a reflection of such a situation. The demand of herbal remedies as psychotherapeutics is greater than ever, having great growth potential in the global market (Dahanukar and Kulkarni, 2000). Several herbs have been used traditionally as brain or nerve tonics. Currently, three of the most popular of these neurotonics are *Bacopa monniera* (BM), *Centella asiatica* (CA) and *Curcuma longa* (CL) (Stafford et al., 2008; Husain et al., 2007; Vaidya, 1997), the plants selected for present studies are commonly available in India, frequently utilized therapeutically and evidently considered as important herbs for the treatment of CNS related disorders in Ayurveda. Various neuropsychopharmacological investigations have been carried out utilizing the extracts of the same (Husain et al., 2007). In view of the versatile medicinal properties of these plants, their therapeutic use has been sharply increasing, thus leading to an over exploitation of these psychotropic herbs, which are among the most popular on the market and naturally have the potential for being overused, abused and thus having increased probability of side effects. To worsen the scenario, many people do take these alternative therapies coupled with conventional medicine, unaware of the consequences. In view of all of the above observations, we wondered if there is a possibility of interactions between these three widely utilized neurotonic plants mentioned above along with the synthetic antidepressants, when ingested concurrently.

**Need of the present study**

The issue of potential interactions between herbs and drugs is of utmost interest now as the use of plants as a source of medicine is an innate and an important component of the health care system in India, a country enriched with large bio diversity (Mathur, 2003; Wakdikar, 2004). Even in this day of increasing spread of allopathic medicines, there are hundreds of millions of people in India who are dependent on biodiversity for their health needs. It is a tradition that is of remarkable contemporary relevance for ensuring health security to the teeming millions. The Indian system of medicine has identified 1,500 medicinal plants of which 500 are commonly used (Agrawal et al.,
It is estimated that there are over 7800 medicinal drug-manufacturing units in India, which consume about 2000 tones of herbs annually (Ramakrishnappa, 2003). There are estimated to be around 25,000 effective plant-based formulations, used in folk medicine and known to rural communities in India. In spite of widespread use of herbal remedies, scientific data about their safety and efficacy are lacking in most cases plus reporting of adverse drug events is currently limited. To worsen the scenario, in the Indian systems of medicine, most practitioners formulate and dispense their own recipes which are available without prescriptions. The same require proper documentation and research. The lack of available clinical data for many herbal products serves as a barrier for post marketing safety assessment of herbal products (Chavez et al., 2006). "Herb-drug interactions occur but are under-researched. In many cases there is no plausible mechanism to explain the observed phenomena and causality is uncertain," said one report (Fugh-Berman, 2000; Fugh-Berman and Ernst, 2001) and hence, interactions between herbs and the conventional drugs need to be addressed and reviewed properly.

We have taken up this study in order to review various aspects of herbal drug interactions to consolidate clinical and pharmacologic aspects of the same and to develop a compendium of information measure of the risk involved via a new insight on safety and mechanisms of some potential herbal drug interactions which are clinically relevant, based on preclinical studies in the laboratory. We reviewed the literature extensively in this area. A literature survey was carried out to compile information about herbal drug interactions as per the guidelines given for the electronic and internet media (Silberg et al., 2007; Wootton 2004; Winker et al., 2000; Eysenback and Diepgen, 1998). A high quality and reliable medical information from the internet was retrieved only from the Health-on-Net (HON) conduct-certified and accredited websites like Entrez PubMed [Medline], CAM-PubMed, Allied and Complementary Medicine Database, Natural Medicine Comprehensive Database, Embase and Cochrane library, apart from the hand-picked research articles from library.
The data bases were searched up to the year 2009. After in-depth analysis and optimization of data, based on the same, we compared and consolidated the information, selected the plants for studies along with synthetic drugs and the parameters were set down for the studies.

Plan of Study

I. Literature review: A comprehensive review was undertaken on all contemporary literature available related to the herbal drug interactions, pharmacognostical and pharmacological profiles of selected herbs, *Bacopa monniera*, *Centella asiatica*, *Curcuma longa* and that of antidepressant models in rodents, attempted in the study.

II. Laboratory studies: Deals with the evaluation of herb and drug combinations for the following activities:

- Gross Behaviour
- Locomotor activity
- Open field Behaviour
- Motor coordination
- Forced swimming test
- Tail suspension test
- Chronic fatigue test
- Biochemical analysis: Determination of adrenalin, noradrenalin and serotonin

III. Results: To record the parameters observed during studies.

IV. Discussion or analysis of the represented data

V. Summary and conclusion derived from overall study.

VI. References.

Based on the data generated, this dissertation has been prepared. The thesis is divided into Part-1- Literature Review with chapter-1, devoted for general introduction, aims and objectives; Chapter-2- assigned to the profiles of the plants selected for the study.
and Chapter -3- allocated to the compilation of information and critical analysis of animal models for depression.

Part-II is devoted to the description of the materials and methods employed in the study. Part-III- deals with presentation of results and observations. Part-IV is concerned with discussion of the observations made and the inference drawn and Part-V provides summary and conclusions. References are listed at the end of the dissertation in part VI followed by the list of publications in national or international journals and the papers, based on the data from results obtained in the present study, presented at various national and international conferences.