2. INTRODUCTION

2.1- History of herbal medicine

India is the largest producer of medicinal herbs and is rightly called the "Botonical garden of the world". There are very few plants of commercial importance, which are not collected or cultivated in this country. Medicinal plants have been in use for thousands of years, in one form or the other, under the indigenous systems of medicine like Ayurveda, Siddha and Unani. Since Independence in 1947, India has made tremendous progress in agrotechnology, process technology, standardization, quality control, research and development etc. Research and Development is an integral part of any industry and herbal drug industry is no exception. Guggulipid, Neem products, Vincristine, Vinblastine, Sennosides, Psyllium husk, Reserpine and many others have achieved international recognition. India is one of the world's 12 leading biodiversity centers with the presence of over 45,000 different plant species (Chaudhari, 1988). Not so many years ago the advances being made in medicine and the innovation of the pharmaceutical industry made it seem inevitable that the use of herbal remedies in developed countries would decline to insignificance. In the early 19th century, when methods of chemical analysis first became available, scientists began extracting and modifying the active ingredients from plants. Later, chemists began making their own version of plant compounds, beginning the transition from raw herbs to synthetic pharmaceuticals. Over time, the use of herbal medicines declined in favor of pharmaceuticals.

It is some what of a paradox, therefore, that at a time when there is an unprecedented number of therapeutic drugs available for the treatment of all forms of disease that herbal medicines continue to be demanded by the general public, which has been steadily increased over the past decade (Carol *et al.*, 1996). Millions of the people in the third world opt for herbal medicines because they believe in them. They also regard them as their system of medicine. It has often been stated that people prefer herbal medicines because it is cheaper. About 80% of 4000 million inhabitants of the world rely on herbal medicines for their first kind of health care because they cannot afford allopathic medicines. This may not be a correct assessment of actual situation. Many of those persons using herbal medicines would continue to use these even if the prices of allopathic medicines come down. Many people in Europe, the United Kingdom and the United States of America are turning to alternative medicine because of the side effects induced by powerful synthetic allopathic drugs. Several of the very important useful medicines we use today come from plants. Many of these have now been synthesized and the synthetic drugs are used. In other instances it is easier to obtain from plants even if these can be synthesized. Some of these medicines are ephedrine, morphine, quinine, emetine, reserpine, digitalis, ergot and vincristine (Chaudhury, 1990). Herbal medicine, also called botanical medicine or phytomedicine, refers to the use of any plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Long practiced outside of conventional medicine, herbal therapy is becoming more focussed as up-to-date analysis and research show their value in the treatment and prevention of disease.

2.1.1 - How are herbs used?

For most herbs, the specific ingredient that causes a therapeutic effect is not known. Whole herbs contain many ingredients, and it is likely that they work together to produce the desired medicinal effect. For these reasons, people prefer using whole plants rather than extracting single components from them. Whole plant extracts have many components. These components work together to produce therapeutic effects and also lessen the chances of side effects from any one component. Several herbs are often used together to enhance effectiveness and synergistic actions and to reduce toxicity. The treatment goals are often more broad than stopping a single complaint. Herbal therapy aims to correct imbalances, resolve patterns of dysfunction, and treat the underlying cause of complaint. Specific symptoms may also be treated if necessary. It also recommends one or more herbs, dietary changes, and lifestyle modifications. Herbal medicines are slower acting than pharmaceuticals. Herbal dosage is a difficult concept to grasp; partly, this is because of the limitations in our knowledge about the herbs, but it is also the result of variations in our concepts of how herbs may contribute to health. For example, we have our own limitations because we often do not know the identity of the main active constituents or their quantities, nor how those quantities might vary among samples of the raw materials, or how they might be affected by the way the herbs are prepared. As to conceptual framework, some people think of herb action in terms of "energetics" in which the quantity of the herb might not be critical; this is an unorthodox idea, one, which has influenced western practitioners via homeopathy. By contrast, many people would think of herbs in terms of the pharmacological effects of the main active ingredients, in which case a certain dosage range will yield those effects, but lower doses may fail to give the desired results; this is a modern scientific viewpoint. In fact, many people don't give much thought to the question of dosage. An added complication is that both the traditional and modern methods of preparation of herbs are sometimes selected on the basis of what is technologically feasible, what is convenient, or what is affordable, rather than what might be ideal from the consideration of traditional practices or clinical efficacy. Decoctions, dried decoctions, powders, dried extracts, tinctures, and pills are some of the dosage forms of herbs.

2.1.2 - Differences from conventional drug use

Although superficially similar, herbal medicine and conventional pharmacotherapy have three important differences:

- ***Use of whole plants*:** People generally use unpurified plant extracts containing several different constituents. They claim that these can work together synergistically so that the effect of the whole herb is greater than the summed effects of its components. They also claim that toxicity is reduced when whole herbs are used instead of isolated active ingredients ("buffering"). Although two samples of a particular herbal drug may contain constituent compounds in different proportions, practitioners claim that this does not generally cause clinical problems. There is some experimental evidence for synergy and buffering in certain whole plant preparations, but how far this is generalisable to all herbal products is not known.
- ***Herb combining*:** Often, several different herbs are used together. Practitioners say that the principles of synergy and buffering apply to combinations of plants and claim that combining herbs improves efficacy and reduces adverse effects. This contrasts with conventional practice, where polypharmacy is generally avoided whenever possible.
- ***Diagnosis*:** Herbal practitioners use different diagnostic principles from conventional practitioners. For example, when treating arthritis, they might observe, "underfunctioning of a patient's systems of elimination" and decide that the arthritis results from "an accumulation of metabolic waste products." A diuretic, choleretic, or laxative combination of herbs might then be prescribed alongside herbs with anti-inflammatory properties.

- ***Polyvalency***: Many herbs contain a wide range of active ingredients, which act in a variety of ways rather than just at one receptor — the concept of herbal polyvalency. A good example would be mistletoe (*Viscum album*), which is one of the most widely, used oncological treatments in Germany. Its various active ingredients prevent DNA/RNA synthesis; stimulate the production of natural T killer cells and cytokines such as interleukins 1 and 6 and TNF-α. It works with the body's immune system rather than against it.

2.1.3 - Some Advantages of Herbal Remedies

Herbal remedies cost less than medicines, and are certainly much more convenient. One of the good things about herbals and dietary supplements is that the patient is empowered. One advantage is wide availability and simple preparation. One can purchase herbal supplements even without a prescription. Most herbs can be prepared with means we all have access to, such as making teas, extracting with alcohol, or similar. This is a large factor in cost of treatment. Herbs are also very well researched. If we pool the knowledge from diverse traditions, we have a cure for just about every illness known to man. Moreover herbs have been around in nature for millennia and our bodies are - one way or another accustomed to their presence. Pharmaceutical medicines on the other hand often introduce a completely new molecule that has never before been present, and it is difficult to predict (or find out without widespread use) what the exact effects are. The FDA regulates medicines, which are one of the most UNSAFE product categories in existence, to where they have become a major cause of concern. Herbs, on the other hand, are ultra-safe by comparison. Herbal medicine has a better future. The importance of traditional system of medicine and of certain traditional medical practices has now been recognized all over the world. Among the various systems of traditional medicines, Ayurveda stand out distinctly as not only a system of great antiquity but an organized system with distinct aims and objectives (Satyavati, 1982). According to the World Health Organisation, herbal (traditional) medicine is used by 80 % of Africans and large sections of the world population rely on it as their primary form of health care. Up to 25% of all prescriptions in Europe and America, contain plant products, which were originally derived from plants (Patil *et al.*, 2005). Pharmaceutical medicine is either going to be deeply reformed or it will die. Once awareness spreads of the amount of damage being done in the name of pharmaceutical medicine, there will be a widespread move away from it, towards more gentle and safer forms of medical care. Bad experiences with herbal medicine seem to be extremely rare by comparison. Herbal remedies are infinitely safer than allopathic medicines. There is really no comparison in seriousness and number of cases of side effects. There are several disorders, wherein allopathic treatment results in serious side effects. Moreover some of the disorders like anxiety, hypertension, and depression are not completely cured by allopathic therapy. Many still rely on indigenous formulation.

2.2 - Anxiety

Anxiety is a normal emotion when it is appropriate to the environmental situation. Inappropriate or pathological anxiety is a well-recognised and common condition, which causes considerable distress to individuals, families and society in general. Anxiety disorders present in a number of forms, although, probably, all share a number of common neurological circuits. While certain psychological treatments are of proven efficacy (Beck *et al.*, 1988) pharmacotherapy remains the most widespread and efficacious treatment, especially in severe cases. Anxiety has evolved biologically as a functional state and, therefore, is both normal and pathological. Furthermore, it can be both a symptom of a wider psychiatric disorder and the primary disturbance in a group of similar, but distinguishable, illnesses, the `anxiety disorders.' Normal anxiety has evolved as a way of controlling an animal's response to threatening or potentially threatening stimuli. This is not just through the classic three 'canonical' options of fight, flight, or freeze (Cannon, 1929), but also through approach avoidance, anticipatory fear, and the generally increased levels of arousal and performance that accompany high normal levels of anxiety (Yerkes, 1921). The concept of a graded progression from functionally useful arousal through to disruptive and maladaptive anxiety has appeal, and it could be argued that pathological anxiety is essentially a maladaptive level of arousal. Unfortunately, there is increasing evidence that what we broadly call anxiety, from a neurobiological viewpoint, may not be a unitary concept. Anxiety varies not just in time and intensity, but also in quality. Free-floating worry is somewhat different from the fearful anticipation of unwanted challenges, which is similarly different from the intense, short lived, unpredictable, and irrational paroxysm of a panic attack. These are normal responses under the appropriate conditions, but pathological and maladaptive if incongruent to the situation. These phenomenological differences to some extent are backed up by differences in physiological changes (Garvey *et al.*, 1987; Klein, 1993), biological markers, and pharmacological response (Argyropoulos *et al.*, 1999), and have led psychiatrists to a more detailed way to describe and operationalise the individual symptoms of anxiety.

This has led to a classification of anxiety disorders based on symptom patterns. Taking into account the phenomenology (intensity, length, quality, and natural history of anxiety symptoms), along with differences in biology (genetics, physiological markers, and pharmacological responses), psychiatrists have constructed syndromes that now constitute a widely accepted typology. Both the DSM-IV (Diagnostic and statistical manual of mental disorders-IV edition)(American Psychiatric Association, 1994) and the ICD-10 (International classification of diseases-10th revision) (World Health Organization, 1992) have similar subgroups (Table 5).

Table 5

Classification of anxiety disorders according to ICD-10 and DSM-IV systems

DSM-IV (American Psychiatric Association)/ anxiety disorders	ICD-10 (World Health Organization)/ neurotic stress, and somatoform disorders
Panic disorder without agoraphobia	Panic disorder
Panic disorder with agoraphobia	Agoraphobia with panic disorder
Agoraphobia	Agoraphobia without panic disorder
Specific phobia	Specific phobia
Social phobia (also known as social anxiety disorder)	Social phobia
Generalized anxiety disorder-GAD	Generalized anxiety disorder Mixed anxiety and depression disorder
Obsessive compulsive disorder-OCD	Obsessive compulsive disorder
Acute stress disorder	Acute stress disorder
Post traumatic stress disorder-PTSD	PTSD Adjustment disorder

2.2.1 - Neuroanatomy of anxiety

The potential role of 5-hydroxytryptamine (5-HT) in anxiety has been the subject of an impressive amount of investigation, most of it addressed to the hypothesis that 5-HT promotes anxiety and, therefore, drugs that reduce 5-HT function will be effective anxiolytic agents in human anxiety disorders (Iversen, 1984; Chopin and Briley, 1987; Traber and Glaser, 1987; Kennett, 1991). Yet, results are beginning to accumulate that a group of drugs that increase 5-HT function, the selective serotonin reuptake inhibitors (SSRIs), are actually effective in anxiety disorders, with a broader spectrum of action than the benzodiazepines. What does this mean for theories of 5-HT function in anxiety? There have been recent developments in understanding the neurobiology of mammalian responses to threatening stimuli. There is also increasing understanding of the characteristics of 5-HT neurons-what their firing patterns are, what receptor subtypes are involved and how 5-HT transmission is controlled. New and powerful tools, such as *in- vivo* dialysis in the behaving animal, studies on knock out - animals (genetically mutated animals with specific genes inactivated) and radiolabelled techniques have been introduced.

2.2.2 - Anxiety models in animals

Anxiety is a common emotion in humans and can be expressed with words. We do not know animals' words but can understand that they have a variety of feelings, including anxiety, by observing their behaviour. Attempts have been made to analyse anxiety by observing animal's behaviour in an artificial environment, which were classified into two different types: with the use or without the use of punishment. Geller and Seifter experimentally created a conflict state in rats by using food pellets (positive reinforcer) and electrical foot shock (punishment) (Geller and Seifter, 1960). Through lever pressing hungry rats were trained to take food pellets with and without an electric footshock. The rats' distress state to press or not to press the lever caused by fear of punishment is thought to be similar to conflict state in humans, *i.e.*, anxiety. Clinically effective anxiolytics suppressed the conflict state in rats, causing them to press the lever more frequently inspite of an electric shock.
Vogel *et al.* also created a similar conflict state in thirsty rats by using two different stimuli, water and electric shock (Vogel *et al.*, 1971). With their methods rodents were motivated by restraint of physiological desire, namely food or water deprivation, to want the positive reinforcement. Similar methods measuring anxiety based on punished behaviour have been performed in other animals such as pigeons and monkeys (Howard and Pollard, 1991).
Another approach to analyse anxiety in rodents is based on exploratory behaviour by creating a conflict between their aversion to special environment and their desire for exploration without food or water deprivation. Different models of anxiety are shown in Table 6.

Table 6

Different models of anxiety behaviour in rodents (Bhattacharya and Satyan, 1997)

I UNCONDITIONED BEHAVIOUR

A. Exploratory behaviour:
   - i. Elevated plus maze
   - ii. Zero maze test
   - iii. Open field test
   - iv. Staircase test
   - v. Hole board test
   - vi. Light- dark exploration
   - vii. Latency to enter mirrored chamber test

B. Social Interaction test

C. Conflict models:
   - i. Geller -Seifter test
   - ii. Vogel's test
   - iii. Four - plate test

D. Miscellaneous tests:
   - i. Novelty induced suppression of feeding and drinking
   - ii. Defensive burying test
   - iii. Cork-gnawing test
   - iv. Defeat-induced analgesia
   - v. Ultrasonic pup vocalization
   - vi. Footshock induced 'freeze' test
   - vii. Antiagression test
   - viii. Antistress test
   - ix. Drug withdrawl-induced anxiety
   - x. Proconvulsant and anticonvulsant activity.

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II CONDITIONED BEHAVIOUR

i Passive avoidance

ii Active avoidance

iii Conditioned emotional response

iv Conditioned place preference

v Conditioned defensive burying

vi Suppression of discriminative learning

vii Conditioned taste aversion

viii Drug discrimination

2.2.3 - Some Behavioral paradigms to model anxiety

Elevated plus maze

Out of many possibilities to modify maze tests e.g. water maze (Morris, 1981; Danks *et al.*, 1991), the Y-maze, the radial maze (Di Cicco, 1991), and the elevated plus maze (Montgomery, 1958; Pellow *et al.*, 1985; Corbett *et al.*, 1991; Lister, 1987) have found acceptance in many laboratories. The test has been proposed for selective identification of anxiolytic and anxiogenic drugs. Anxiolytic compounds, by decreasing anxiety, increase the open arm exploration time; anxiogenic compounds have the opposite effect.

Hole board test

The evaluation of certain components of behavior of mice such as curiosity or exploration has been attempted by Boissier *et al.* (1964) and Boissier and Simon (1964). They used an open field with holes on the bottom into which the animals could poke their noses. Poking the nose into a hole is a typical behavior of mice indicating a certain degree of curiosity. Evaluation of this component of behavior has been proven to be quite useful. Benzodiazepines tend to suppress nose poking at relatively low doses.

Light Dark model

Crawley and Goodwin (1980); Crawley (1981) described a simple behavior model in mice to detect compounds with anxiolytic effects. Mice and rats tend to explore a novel environment, but to retreat from the aversive properties of a brightly lit open field. In a two-chambered system, where the animals can freely move between a brightly lit open field and a dark corner, they show more crossings between the two chambers and more loco motor activity after treatment with anxiolytics. The numbers of crossings between the light and dark sites are recorded.

Open field test

Interruption of light beams as a measure of movements of rats or mice in a cage (open field) has been used by many authors such as Dews (1953), Nakatsu and Owen, (1980). Recently developed devices allow registering not only general motor activity but also locomotion, rearing and the speed of locomotion (Barros *et al.*, 1991; Ericson *et al.*, 1991).

Staircase test

The staircase test for evaluating anxiolytic activity was originally described for rats by Thiebot *et al.,* (1973). When introduced into a novel environment, rodents experience a conflict between anxiety and exploratory behavior manifested by increased vigilance and behavioral activity. In the staircase paradigm, step climbing is purported to reflect exploratory or locomotor activity, while rearing behavior is an index of anxiety state. The number of rearings and steps climbed are recorded in a 5 min period. The dissociation of these parameters is considered to be characteristic for anxiolytic drugs. The test was modified for rapid screening of anxiolytic activity in mice (Simiand *et al.*, 1984).

The elevated T-maze

To test this dual 5-HT-fear hypothesis, a new animal model of anxiety, named the elevated T-maze, was developed (Graeff *et al.*, 1993; Viana *et al.*, 1994). The aim was to generate conditioned and unconditioned fear in the same rat. The apparatus is derived from the elevated x or plus-maze (Handley and Mithani, 1984; Pellow *et al.*, 1985), a widely used animal model of anxiety.

2.3 - Hypertension

Hypertension, an elevated arterial blood pressure, is the most common cardiovascular disease and a major public health issue in developed as well as developing countries. Although it is common and readily detectable, it can often lead to lethal complications if left untreated. Hypertension is usually defined as sustained elevation of systolic blood pressure ≥140 mm Hg or of diastolic blood pressure ≥90 mm Hg. It is major risk factor for CAD (coronary artery disease) and stroke and a leading cause of death worldwide. An elevated arterial blood pressure is probably the most important public health problem. It is common, a symptomatic, readily detectable, and usually easily treatable, often leads to lethal complications if left untreated. As a result of extensive educational programs in the late 1960s and 1970s by both private and government agencies, the number of undiagnosed and/or untreated patients was reduced significantly by the late 1980s to a level about 25%, with a concomitant decline in cardiovascular mortality. Unfortunately, by the mid 1990s, this beneficial trend began to wane. The number of undiagnosed patients with hypertension increased to nearly 33%, the decline in cardiovascular mortality flattened, and the number of individuals with chronic diseases with untreated or poorly treated hypertension increased. For example, the prevalence of end stage renal disease per million population increased from < 100 in 1982 to > 250 in 1995, and the prevalence of congestive heart failure from age of 55 to 75 was more than double between 1976 to 1980 and 1988 to 1991.

Thus although our understanding of the pathophysiology of elevated arterial pressure has increased, in 90 to 95% of cases the etiology (and thus potentially the means of prevention or cure) is still largely unknown. As a consequence in most cases the hypertension is treated nonspecifically, resulting in a large number of minor side effects and a relatively high (50-60%) noncompliance rate. The classification of blood pressure in case of adults and classification of arterial blood pressure has been presented in Table7 and Table8 respectively.

Table 7

Classification of blood pressure for adults

Type	SBP (mm Hg)	DBP (mm Hg)
Normal	120	< 80
Prehypertension	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	≥ 160	or ≥ 100

(Taken from The Merck Manual, Table 199-2, Ch. 199, Arterial hypertension)

Factors that are associated with an increase in blood pressure include obesity, physical inactivity, excessive alcohol use, and excessive salt intake. Obesity and sedentary lifestyles are increasing in many societies and are becoming a particular problem in young people. Hypertension affects approximately 50 million individuals in the United States and approximately one billion worldwide. As the population ages, the prevalence of hypertension will increase even further unless broad and effective preventive measures are implemented. The rising use of alcohol in various population groups and a "western-style" salt rich diet are also contributing to a potential epidemic of high blood pressure. Blood pressure rises inevitably with age in such populations; two thirds of people above the age of 65 years in both the UK and US have hypertension. There is no room of complacency: recent data from the Framingham Heart Study suggest – "individuals who are normotensive at age 55 have a 90 percent lifetime risk for developing hypertension" (from JNC-VII, 2003). On average, just over half of all people with hypertension are actually aware of their condition; only half of these people are receiving treatment and, of these less than half achieve adequate blood pressure control. In other words only one person of eight with hypertension is treated and controlled, leaving the overwhelming majority of hypertensives with a substantial unmet clinical need.

It is difficult to obtain mortality data purely on hypertension; mortality and morbidity figures are more commonly given for cardiovascular disease as a whole, or for CAD and stroke. This will serve to underestimate the true impact of hypertension, since death may be attributed to the consequent cardiovascular event as opposed to the underlying hypertension. It has been estimated that 70% of the patients with hypertension will die as a consequence of their elevated blood pressure.

The goal of treating elevated blood pressure is to prevent cardiovascular events. The risk of cardiovascular disease begins at 140/ 90 Hg and doubles with each increment of 20/ 10 mm Hg. For any individual, treatment should be considered at that level of blood pressure where investigation and treatment do more good than harm. This level will be dictated by co-existing risk of vascular disease. Because of its high incidence and morbidity, various classes of drugs and regimens have been advocated for the control of hypertension. Despite the large treatment of hypertension, the last two decades have witnessed the introduction of a number of new antihypertensive drugs. Recent research during this period has also added considerably to our knowledge of the mechanisms involved in the pathogenesis of hypertension. High blood pressure can often be alleviated through simple changes in diet and lifestyle. In fact, changing diet alone has proven as effective as many drug therapies in reducing blood pressure. Nonetheless, doctors continue to prescribe drugs with dangerous side effects to countless subjects with hypertension.

Table 8

Classification of arterial hypertension (Kuntz, 1970)

I. Systolic Hypertension with wide pulse pressure:

- Decreased compliance of aorta
- Increased stroke volume
- Aortic regurgitation
- Thyrotoxicosis
- Hyperkinetic Heart Syndrome
- Arteriovenous fistula
- Patent ductus arteriosus

II. Systolic and diastolic hypertension (Increased peripheral vascular resistance)

1. Renal:
   - Chronic pyelonephritis

- Acute and chronic glomerulonephritis
- Polycystic renal disease
- Renovascular stenosis or renal infarction
- Most other severe renal diseases (arteriolar nephrosclerosis, diabetic Nephropathy, etc.)
- Renin producing tumor

2. Endocrine:
   - Oral contraceptives
   - Adrenocortical hyper function
   - Cushing's disease and syndrome
   - Primary hyperaldosteronism
   - Congenital or hereditary adrenogenital syndromes (17 α-hydroxylase and 11β-hydroxilase defects)
   - Pheocromocytoma
   - Myexedema
   - Acromegaly
3. Neurogenic:
   - Psychogenic
   - Diencephalic syndrome
   - Familial dysautonomia (Riley-day)
   - Polyneuritis (acute porphyria,lead poisoning)
   - Increased intracranial pressure (acute)
   - Spinal cord section (acute)
4. Miscellaneous:
   - Coarctation of aorta
   - Increased intravascular volume (excessive transfusion)
   - Polycythemia vera
   - Polyarteritis nodosa
   - Hypercalcemia
   - Medications, e.g. glucocorticoids, cyclosporine
5. Unknown etiology:
   - Essential hypertension (90% of all cases of hypertension)

- Toxemia of pregnancy
- Acute intermittent porphyria

2.3.1 - How modern treatments of hypertension fail? (IASH- The Inter-American society of hypertension)

Even though diet has been shown to be as effective as drug therapies in reducing high blood pressure, many patients are still given prescription drugs for hypertension. These drugs, including beta-blockers and diuretics are the most widely prescribed drugs. They lower blood pressure by decreasing heart rate, cardiac output and peripheral resistance. Their side effects are numerous: congestive heart failure, lightheadedness, depression, fatigue, and sexual impotence. They are also known to increase levels of cholesterol and triglycerides in the blood and long-term use can result in diabetes. Diuretics promote the excretion of minerals like calcium and magnesium, which have been shown to be effective agents in lowering high blood pressure and preventing heart attacks.

2.3.2 - Hypertension models in animals

Human essential hypertension is a complex, multifactorial, quantitative trait under polygenic control. In order to understand the pathogenesis and to study the treatment and prevention of a disease, it is useful to develop animal models. Various models of experimental hypertension have been primarily developed to obtain information on the etiopathogenesis of hypertension. These models are also used in the pharmacological screening of potential antihypertensive agents. In the past, hypertensive animal models have been used infrequently for testing antihypertensive potential of drugs. As new molecules are being synthesized in a large number, the use of animal models is increasing for testing these molecules. New animal models of hypertension are being developed as new insights in to the pathogenesis of hypertension are revealed.

The animal models of hypertension share many features that are common to human hypertension. Many of these models have been developed by utilizing the etiological factors that are presumed to be responsible for human hypertension such as excessive salt intake, hyperactivity of renin angiotensin-aldosterone system (RAAS) and genetic factors. Since regulation of blood pressure (BP) is multifactorial, the effectiveness of an antihypertensive agent in one model does not necessarily mean that the mechanism of action of a given agent in a given model is related to the pathogenesis of elevated blood pressure.

An ideal animal model of hypertension should fulfill the following criteria:

- It should be feasible in small animals.
- It should be simple to perform and uniformly reproducible.
- It should be able to predict the potential antihypertensive properties of an agent.
- It should consume minimal quantities of compounds.
- It should be comparable to some form of human hypertension.

Whereas in the past, most studies on experimental hypertension were carried out on dogs, currently rat is the preferred animal species. Spontaneous hypertensive rat (SHR), the genetic strain of hypertensive rat, is the animal of choice for screening antihypertensive agents. SHR is the cornerstone of medical research in experimental hypertension. Rabbits, monkeys, pigs and mice are also used to produce experimental hypertension.

2.3.3 - Some animal models of hypertension commonly used include

1. Renovascular hypertension
2. Dietary hypertension
3. Endocrine hypertension
4. Neurogenic hypertension
5. Psychogenic hypertension
6. Genetic hypertension
7. Other models:
    - Obesity related hypertension
    - Hypertension induced by cholinomimetic agents
    - Angiotensin II induced hypertension
    - Hypertension induced by cadmium
    - Chronic nitric oxide inhibition induced hypertension
    - Transgenic rat (TGR) models
    - Uterine Ischemia

Thus, to summarize, anxiety is the psychological counterpart of normal fear. It is not only a cardinal symptom of many psychiatric disorders but also an inevitable component of many medical and surgical conditions. It is the most common suffering manifested as disturbances in sleep, thinking, mood, irritability and marked changes in the normal physiological actions. The etiology of most anxiety disorders although not fully understood, it has become an area of sharper focus in the recent past. Anxiety is a universal human emotion and is commonly associated with depression, phobias, panic, agoraphobia, eating and personality disorders. As per Internet mental health, 5-15% of the world population will suffer from anxiety related disorders. 3-5% shall suffer from GAD. It is more common in women than in men (3.5:1). OCD usually occurs earlier in males (6-15 years) than in females (20-29 years). A study showed that 35% patients with pulmonary hypertension suffered from mental disorders with the most common being major depressive disorder (15.9%) and panic disorder (10.4%) (Berndlowe *et al.*, 2004). In United States, the frequency of attacks of panic disorder is roughly 1.5-3.5 % of which one third to one half also have agoraphobia; major depressive disorders is 50-65%; phobic disorders is 10-13%. But the good news is that anxiety is the most treatable of all psychological conditions.

It is extremely difficult to escape stress looking at the existing hurried lifestyle of mankind. Not many herbal anxiolytics are available in the market presently. The marketed anxiolytic agents like diazepam, chlordiazepoxide have several adverse effects including one on memory. It is therefore essential to have an anxiolytic agent having minimal side effects and not impairing cognitive functions. Since increased stimulation of serotonergic or sympathetic pathway also leads to anxiety, we wished to study the involvement of 5-HT/ noradrenergic system in anxiolytic activity mediated by the active component(s) of the selected plants. The prevalence of population suffering from stress related disorders clubbed with hypertension is quite alarming. The role of anxiety and tension in hypertension has long been a subject of debate; patient commonly thinks that tension part of the word in hypertension refers to a psychic rather than physical phenomenon. The constellation of symptoms in many of these patients described includes paresthesia, lightheadedness, dizziness, palpitations and headache. A survey conducted showed a significant higher prevelance of panic attacks in hypertensive rather than normotensive patients (30% vs 19%) (Thomas, 2000). In search for alternatives to antihypertensive drugs, the 5-HT_3 receptor antagonists are currently being considered for their potential use in hypertension (Tsukomoto *et al.,* 2000).

Moreover plant-derived drugs are considered by analysts to be a viable alternative to the chemically based pharmaceutical industry. The synergistic components found in botanical mixtures represent a largely untapped source of new pharmaceutical products with novel and multiple mechanisms of action. Recent developments in plant biotechnology have created the tools to produce botanical mixtures at a level comparable to that of pure drug compounds. The thinking is that botanical drug products will ultimately compete along side conventional pharmaceuticals in the $300 billion global pharmaceutical marketplace.

Numerous plants have been reported to possess anxiolytic activity. Saponins from *Albizzia lebbeck* (Une *et al.,* 2001), saponins from *Bacopa monniera* (Bhattacharya and Ghosal, 1998), gingerols from *Zingiber officinale* (Vishwakarma *et al.*, 2002), triterpenes from *Sesbania grandiflora* (Kasture *et al.*, 2002) are the active principles mediating anxiolytic effects. Plants containing alkaloids like Passionflower, *Turnera aphrodisiaca* have been reported to possess anti-anxiety effects (Kumar and Sharma, 2005; Elisabetsky and Costa, 2006; Cronin, 2003).

Plants selected for the study include –

(a) *Trigonella foenum graecum* (seeds)

(b) *Zingiber officinale* (dried rhizome)

(c) *Panax pseudoginseng* (Indian variety)(rhizome) and *Korean ginseng* (roots).

In all the studies reported in this thesis we have compared the effects of Indian variety of ginseng- *Panax pseudoginseng* extract with a typical known anxiolytic of its Korean counterpart – *Korean ginseng.*

Literature survey has indicated that their anxiolytic and antihypertensive actions these plants have not been explored much. Although the claims made about herbs in the official books of ayurveda in humans have been confirmed their mode of action and evaluation still needs to be established. A similar evaluation using the above plant extracts in animals for their anxiolytic and antihypertensive properties was initially proposed. Moreover the above herbal plant parts are commonly used as one of the condiments in regular household diet. Being easily accessible, this has further attracted us to direct our work using these commonly available plant species. Thus the objective of the present work is to establish the predicted actions and provide an insight on the mode of action of the selected plants.

An extensive literature survey on the above plants suggested that:

a. ***Trigonella foenum graecum*** is well known for its appetite stimulant properties whose effect is mediated through 5-HT receptors. It also has antifatigue effects. Ghosal *et al.*, 1974 has worked on its antihypertensive effects without emphasizing on its 5-HT mechanism. Moreover, it is well known that a rise in endogenous 5-HT levels leads to anxiety and viceversa. This led to a hypothesis that anxiolytic and antihypertensive effects of this plant could possibly be mediated through its 5-HT mechanism.

b. ***Zingiber officinale*** is well known for its antiemetic effects (Yamahara *et al.*, 1989; Bone *et al.,* 1990) mediated through its 5-HT_3 antagonistic properties. This has prompted us to explore the antihypertensive effects of this plant through its 5-HT_3 antagonistic effects using Phenylbiguanide- a 5-HT_3 agonist, although literature survey has indicated that the aqueous ginger extract and its phenolic constituents lowers BP through a dual inhibitory effect mediated via stimulation of muscarinic receptors and blockade of Ca++ channels (Ghayur *et al.*, 2005).

c. Ginseng, an adaptogenic is also being used as one of the commonly used over the counter herbal prescription in patients with cardiovascular disease (Pharand *et al.,* 2003). Korean red ginseng can improve the vascular endothelial dysfunction in patients with hypertension possibly through increasing the synthesis of nitric oxide (Sung *et al.,* 2000). Scanty work on *Panax pseudoginseng* has been reported with respect to its antihypertensive effects. Although these studies have reported different mechanism for their antihypertensive effects, no mechanistic studies involving the 5-HT have been hypothesised.

In search for better alternatives to antihypertensive drugs, the 5-HT class of drugs; the 5-HT_3 receptor antagonists, 5-HT_{1A} agonist and 5-HT_{2B} antagonists are currently being considered for their potential use in hypertension (Tsukomoto *et al.,* 2000; Shingala and Balaraman, 2005). Reports on anxiolytic studies on the above selected plants are very few (Vishwakarma *et al.*, 2002; Hwa-Young Cha *et al.*, 2004). I, therefore proposed to study anxiety and antihypertensive properties of the above plant species through its possible 5-HT mechanism.

Thus the aims of the thesis with reference to the above-mentioned reviews include:

1. **To extract specific parts of the plants using various solvents.**
2. **To screen the anxiolytic activity of crude extracts using various behavioural paradigms like elevated plus maze, open field apparatus and light dark apparatus.**
3. **To isolate the active component(s) from crude extracts using chromatographic techniques by employing solvents of varying polarity.**
4. **To conduct phytochemical testing of extracts.**
5. **To subject the active fractions to various analytical tools such as HPTLC, GC-MS, LC-MS.**
6. **To evaluate the anxiolytic activity of the different fractions using various models of anxiety.**
7. **To screen the antihypertensive effect of the extracts and their active fractions using invasive blood pressure measurement *i.e* carotid canulation (direct method).**
8. **To evaluate the antihypertensive action of the extracts and their active fractions on experimentally induced hypertensive rats (DOCA model and Fructose model).**
9. **To elucidate the probable mode of action using various agonists and antagonists like *m*-CPP, ondansetron, ketanserin, phenylbiguanide and to carry out additional studies which would support the predicted 5-HT hypothesis like Lithium induced head twitches in rats.**
10. **To perform neuropharmacological tests of extracts and their active fractions.**