INTRODUCTION AND AIM OF THE STUDY

INTRODUCTION

Most of the developing countries and in particular those situated in the tropical belt constitute richest store house of medicinal plants on which the traditional herbal system of medicine has been based and used since ancient times. Inspite of phenomenal development in the synthetic drug industry and antibiotics, medicinal plants still constitute an important part of pharmacopoeias in both the developed and developing countries. India is the largest producer of medicinal herbs and is rightly called the "Botanical garden of the world". India is one of the world's 12 biodiversity centers with the presence of over 45000 different species of plants. Herbal medicines (defined as preparations derived from plants and fungi, for example by alcoholic extraction or decoction, used to prevent and treat diseases) are an essential part of traditional medicine in almost any culture (Vickers A & Zollman CE 1999). In industrialized countries herbal drugs and supplements are an important market. Some countries like Germany have a long tradition in the use of herbal preparations marketed as drugs and figures for prescriptions and sales are stable (Schwabe, U 1999). In the US and the UK herbal medicinal products are marketed as "food supplements" or "botanical medicines". In recent years sales of such products have been increasing strongly (Brevoort P 1998; Barnes, J 2000). In the Third World herbs are mainly used by traditional healers (Bodeker GC 1996).

Advantages of Herbal Remedies

Herbal remedies cost less than medicines and are more convenient. One advantage is wide availability and simple preparation. One can purchase herbal supplement without prescription. Most herbs can be prepared with means we have access to, such as making tea, extracting with alcohol, or similar. Herbs have been around in nature for millennia and our bodies are one way or the other accustomed to their presence. Pharmaceutical molecule on the other hand introduces a completely new molecule that has never been present before and it is difficult to predict what the exact effects are. The importance of traditional system of medicine and certain traditional medical practices have now been recognized all over the world. Among the various systems of traditional systems of medicine, aurveda stand out distinctly not only as system of great antiquity but an organized system with distinct aims and

objectives (Sathyvati 1982).According to the world health organization herbal medicines are used by 80% of Africans and large sections of world populations rely on it as their primary form of health care. Up to 25% of all prescription in Europe and America contain plant products (Patil et al., 2005).People generally use unpurified plant extracts containing several different constituents. They claim that these work together synergistically so that effect of the whole herb is greater than the summed effect of its components. They also claim that toxicity is reduced when whole herbs are used instead of isolated active ingredients. There is some experimental evidence for synergy and buffering in certain whole plant preparations. Several different herbs are used together. Practitioners say that the principle of synergy and buffering may apply to combinations of plants and claim that combining plants improves efficacy and reduces adverse effects.

Herb to lead molecule

Indiscriminate use of synthetic drugs with adverse long term drug reactions has, during the last couple of decades, caused concern and has made the researchers and manufacturers develop safer medicines based on medicinal plants. Scientific studies on medicinal plants in most part of the world have used conventional methods of screening plants for biological activity and for identifying the active principles through phytochemical studies. Systematic scientific investigations carried out on them have since resulted in identification of a growing number of active constituents. Many of these are important part of modern medicine. Some of the well known examples being Reserpine, Atropine, Metformin, Vincamine, Vinblastine, Vincristine, Morphine etc.

Historically, plant drugs have been the mainstay of treatment in India, China and in some other countries. Large numbers of plants are included in clinically useful preparations. Many such preparations are listed in old texts of traditional system of medicine which differ from country to country. Aurvedic system is most prevalent in India. However with the passage of time many of the plant species have become extinct and in many there have been changes due to genetic mutation and the property of such plants may not be the same as they originally had. Also with the development of new technologies physicians are not fully convinced by the traditional use till scientific evidence is provided in terms of modern concept as far as their efficacy and safety is concerned. **It is therefore, imperative that the large wealth of medicinal**

plants is investigated and those found useful may be included in the armamentarium of the physicians.

The Ayurvedic approach to diabetes:

Ayurvedic physicians have treated diabetes for thousands of years using a combination of regulated lifestyle and herbal formulations. The following paragraphs summarizing the description of diabetes mellitus by two ancient Indian physicians are excerpted here from a fairly recent publication on Ayurvedas: "About the one transmitted genetically, Sushruta says "a *person would be diabetic if his father and grandfather are diabetic*". In fact, he mentions that such type of person is clinically diabetic. The genetically transmitted entity of insulin dependent diabetes mellitus is well known today. What is striking is his description of an insulin dependent diabetic whom he describes as a thin, restless individual. The characteristics of diabetes of dietary origin are described to be exactly opposite, which also fit in with the features of Type II mentioned in modern medicine. Charaka too agrees with the genetic origin of diabetes and adds that this type is more difficult to cure. These physicians also prescribed specific herbal formulations for the treatment of diabetes. Some of these herbs, with a record of safety and efficacy are spanning several centuries. In recent times, the safety and efficacy of these herbs have been validated by laboratory experiments and clinical trials.

***Gymnema sylvestre* (Australian Cow Plant)**

The leaves of this plant (referred to in the vernacular as "gur mar" meaning "sugar destroyer"), (Asclepidaceae) have the property of abolishing the taste of sugar. The blood sugar lowering effects of the leaf extracts were further confirmed by researchers who found that damaged islets of langerhans in diabetic rats could be regenerated by administration of GS_4, a standardized extract obtained from *Gymnema sylvestre* leaves (Shanmugasundaram, ERB et al., 1990). This led to the hypothesis that *Gymnema* extracts could induce the pancreas to secrete insulin (Shanmugasundaram, K.R. & Panneerselvam, C. 1981), a finding confirmed by later laboratory experiments and clinical studies on Type I and Type II diabetes patients (Srivatsava, Y. 1985; Shanmugasundaram ERB et al., 1990; Baskaran et al., 1990,).

***Momordica charantia* (Bitter melon)**

The fruits of the plant are well known in Ayurvedic medicine and in folk use as being useful in diabetes management. Laboratory experiments and clinical trials using an extract of the dried fruits from the plant indicate that it lowers blood sugar levels.

In controlled clinical studies, *Momordica charantia* extracts have been shown to significantly lower blood sugar levels, particularly in patients with Type II diabetes. In view of these effects, *Momordica charantia* is a potential herbal alternative in diabetes management, particularly in non-insulin dependent diabetes (Welihinda J et al., 1986; Raman A and Lau C. 1996).

***Trigonella foenum graecum* (Fenugreek)**

A member of the Leguminosae family is a known hypoglycemic agent. Studies have revealed the efficacy of defatted fenugreek seed extracts in the management of both Type I and Type II diabetes (Sharma, RD. 1986; 1990). Administration of defatted fenugreek seed powder for a period of three weeks significantly improved the performance of Type II diabetes patients in the glucose tolerance test. Some of the patients under treatment also reduced their insulin requirements from 56 units per day to 20 units per day. Within the duration of this study, there were no new incidences of heart problems such as angina and myocardial infarction and no increases in blood pressure, indicating that fenugreek may be helpful in preventing the secondary complications of diabetes such as hyperlipidemia and atherosclerosis.

***Pterocarpus marsupium* (Vijayasar)**

Pterocarpus marsupium Roxb. (Family Leguminosae) has been used traditionally in the management of diabetes and hyperlipidemia. *Pterocarpus marsupium* is a rich source of polyphenolic compounds. The key compounds include the diaryl propane derivative, propterol; the stilbene, pterostilbene; the hydrochalcone, pterosupin; the benzofuranone, marsupsin; the flavanoid, liquiritigenin and the catechin, (-)-epicatechin. Of these, the compounds pterostilbene and (-) epicatechin are reported to have blood sugar lowering effects in laboratory studies (Manickam, M et al., 1997). (-)-Epicatechin has also been shown to have an effect on the conversion of proinsulin to insulin (Ahmad, F et al., 1991). *P. marsupium*, alone or as in multi-ingredient formulations, has also been successful in reducing the blood sugar of

diabetic humans. In one laboratory study, pancreatic beta cell regeneration was observed in alloxan-induced diabetic rats that received the flavonoid fraction from the bark of *P. marsupium* (Chakravarthy, BK et al 1980).The Indian Council of Medical Research undertook an anti-diabetic Phase II clinical trial at four centers across India using Vijayasar. Ninety-three of 223 patients admitted for the therapy were evaluated for 12 weeks (ICMR 1998). Patients responded well to the therapy with no untoward side effects. Another clinical study with 20 participants also reported beneficial effects on the symptoms of diabetes (Ojha, J.K. et al., 1978).

***Salacia species (Salacia oblonga, Salacia reticulata)* (Pitika)**

Dried roots of *Salacia reticulata* (family Celastraceae) were found to inhibit alpha-glucosidase enzymes.In the sucrose tolerance test conducted on human volunteers, administration of 200 mg p.o. SRE 5 minutes before sucrose loading (50 g) significantly suppressed postprandial hyperglycemia. Double blind placebo controlled trials on human volunteers with mild Type II diabetes showed promising results (Kajimoto, O et al., 2000; Heacock PM et al 2005).

***Ocimum sanctum* (Tulsi, Holy basil)**

This plant, used in Ayurveda for over 2000 years has now been explored as an adjunct to dietary therapy and drug treatment in mild to moderate Type II diabetes. Results of a single-blind placebo-controlled trial indicated a significant decrease in blood glucose levels during the treatment of Type II diabetes with Tulsi leaves as compared to placebo (Chattopadhyay, RR. 1993).

***Szygium cumini* (*Eugenia jambolana*)**

The fruit kernels of this plant (Java plum, "jamun") have are used traditionally in the management of diabetes. Studies on animal models revealed that extracts from the plant promote insulin secretion in isolated islets of Langerhans and lower blood sugar levels in experimental diabetes (Kedar, P. & Chakrabarti, C.H. 1983; Achrekar S. et al., 1991). The whole fruit powder is traditionally used in mixed formulations for diabetes management.

Scientific basis for using mixed formulations:

Ayurvedic remedies for diabetes are usually mixed formulations(Yajnik, VH et al., 1993; Nair, RB et al., 1992) containing blood sugar lowering herbs in combination with immunomodulators, diuretics and detoxicants. The rationale behind such formulations is provided by modern research, which documents that immune processes play a predominant role in the destruction of beta cells and that free radicals (Oberley, L.W. 1988) feature predominantly in the progression of the disease and its secondary complications. The inclusion of immunomodulators, and detoxifying antioxidants in mixed formulations is therefore beneficial. Some traditional formulations also contain cholesterol reducing agents and adaptogens such as *Emblica officinalis.*

More recent studies provide the link between obesity and the development of Type 2 diabetes. Researchers identified a mechanism that helps to explain how the hormone leptin (originally termed the "satiety signal"), is involved in the metabolism of fatty acids in muscle (Yasuhiko, M et al., 2002). A novel molecular link between obesity and diabetes is thus indicated, suggesting the possibility of a new target for the development of drugs that would help manage both conditions. The potential applications of nutraceuticals in this context cannot be ruled out. For instance, recent studies suggest that *Garcinia cambogia* extract efficiently improved glucose metabolism and displayed leptin-like activity in mice (Hayamizu K et al 2003). *Garcinia cambogia* extract (more accurately, its active compound (-) hydroxycitric acid) is a well known dietary supplement that supports weight loss and healthy body composition. In view of the significance of obesity in the etiology of Type II diabetes, inclusion of herbs such as *Garcinia cambogia* (Hackman, R. 1996) that support weight management may be beneficial if used in combination with conventional drugs such as metformin. Vascular inflammation is now regarded by medical researchers as the key underlying cause for several chronic disease conditions, including diabetes. On a related note, recent research reveals that diabetes raises the risk of gum disease (an inflammatory condition), and the risk of some types of cancer.Anti-inflammatory approaches such as Turmeric root (contains curcuminoids that help in inhibiting COX-2 enzymes), *Commiphora mukul* (Guggul) extract (contains guggulsterones and ferulates that help in reducing markers of inflammation such as C-reactive protein [CRP] in the plasma), and other healthful medicinal plants from Ayurveda, are therefore integrated into diabetes support formulations. These healthful herbs also

support cardiovascular health through their beneficial effects against vascular inflammation.

The following are the Antidiabetic herbs in common use:

Botanical Name	Common Name
Allium cepa	Onion bulbs
Allium sativum	Garlic cloves
Anacardium occidentale	Cashew leaves
Arctium lappa	Burdock roots
Catharanthus roseus	Madagascar Periwinkle leaves
Cuminum cyminum	Cumin seed
Eleutherococcus senticosus	Siberian Ginseng
Galega officinalis	Goat's Rue seeds
Gymnema sylvestre	Gymnema leaves
Momordica charantia	Bitter Melon fruit
Opuntia spp.	Prickly Pear stems and fruit
Panax ginseng	Chinese Ginseng root
Phaseolus vulgaris	Kidney bean, immature pods
Taraxacum officinale	Dandelion plant
Trigonella foenum-graecum	Fenugreek seeds
Urtica dioica	Stinging Nettle plant
Vaccinium myrtillus	Bilberry leaves
Olea europaea	Olive leaves
Oplopanax horridum	Devil's Club root bark
Nymphaea lotus	Lotus roots
Ocimum sanctum	Sacred Basil plant
Oenothera biennis	Evening Primrose leaf
Polygonatum multflorum	Solomon's Seal root
Rhus typhina	Staghorn Sumach leaves
Salpianthus arenarius	Catarinita flowers
Scoparia dulcis	Sweet Broom plant
Securinega virosa	Fluggea seeds
Spinacea oleracea	Spinach leaves

Sarcopoterium spinosum	Thorny Burnet root bark
Psittacanthus calyculatus	Injerto flowers, leaves, and stem
Musa sapientum	Banana flowers and roots
Morus spp	Mulberry leaves
Lycopus virginicus	Bugleweed plant
Lycium barbarum	Box Thorn leaves
Lupinus albus	Lupin seeds
Lagerstroemia speciosa	Lagerstroemia leaves and ripe fruit
Inula helenium	Elecampane root
Hygrophila auriculata	Barleria plant
Hydrastis canadensis	Goldenseal root
Hordeum vulgare	Barley sprouts
Cuminum cyminum	Cumin seed
Cucumis sativus	Cucumber fruit
Coutarea latiflora	Copalchi root bark
Corchorus olitorius	Jute leaves
Coccinia indica	Ivy gourd
Coccinia grandis	Coccinia roots
Cecropia obtusifolia	Guarumo leaves and stem
Brassica oleracia	Cabbage
Blighia sapida	Akee Apple seeds
Bidens pilosa	Aceitilla plant
Atriplex halimus	Salt Bush leaves
Arctium lappa	Burdock roots
Argyreia cuneata	Rivea leaves
Andrographis paniculata	Kirata leaf
Anacardium occidentale	Cashew leaves
Adiantum capillus-veneris	Adiantum plant
Syzygium jambolanum	Jambul seeds
Tecoma stans	Tronadora leaves

Animal models for experimental Diabetes Mellitus

There are many advantages of using animals models in research work on diabetes as various aspects of the disease like the etiology, its multifactorial genetics, pathogenesis of the disease and its complication can be explicity understood. Secondly, it also helps in the development and evaluation of newer agents for the treatment of diabetes. However, there are some limitations in the use of animal model for studies on diabetes. Induction of diabetes in animals can be carried out by various ways – by using different chemical diabetogenic agents, surgically by partial pancreatectomy, by viral induction and genetic manipulation by selective in breeding.

Various diabetic chemicals

Induction of diabetes by various chemical diabetogenic agents is also dependent on the species, the strain, sex and the diet of the animals. Variations in susceptibility have also been observed amongst male and female mice of same strain, males being more susceptible to insulin dependent diabetes mellitus (IDDM) than females. Types of diabetes produced depend on the amount of diabetogenic agent used.

1. Alloxan (Szkudelski T 2001)

Diabetogenic action of alloxan is mediated by reactive oxygen species. Alloxan and the product of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutation to hydrogen peroxide. Thereafter highly reactive hydroxyl radicals are formed by the Fenton reaction. The action of reactive oxygen species with a simultaneous massive increase in cytosolic Ca^{+2} concentrations causes rapid destruction of β-cells. The action of alloxan in the pancreas is preceded by its rapid uptake by the β-cells. Since alloxan exhibits a high affinity to the SH-containing cellular compounds, reduced glutathione (GSH), cysteine and protein bound sulfhydryl groups (including SH-containing enzymes) are very susceptible to its action. The reaction between alloxan and dialuric acid is a process in which intermediate alloxan radicals ($HA^{\cdot}$) and an unidentified "compound 305" (maximum absorption at 305 nm) is formed. Alloxan is converted into unstable dialuric acid which is then reoxidised back to alloxan. This reaction establishes a redox cycle for the generation of superoxide radicals and also

accompanied by reduction of oxygen to the OFR, O_2, and H_2O_2. The latter, through a Fanton Type reaction in the presence of transition metals generates the highly toxic OFR, OH. Increased production of OFR in the islets, together with inadequate defence makes the β-islet cells susceptible to alloxan. Alloxan induces membrane lipid peroxidation and extensive DNA strand breakage in these cells. In normal non fasted animals, the blood glucose level after alloxan injection fluctuates in a triphasic pattern.

Triphasic response of alloxan: Early hyperglycemia of short duration (about 1-4 h) due to a sudden short lasting decrease or cessation of insulin release and a direct glycogenolytic effect on the liver.

1. Hyperglycemia phase lasting up to 48 h and often resulting in convulsion and death (which may be prevented by treatment by glucose) due to uncontrolled leakage of insulin from the damaged cells.
2. Chronic diabetes phase, consequence of insulin lack histologically only a few β-cells if any, are detectable in animals with fully developed alloxan diabetes. Exogeneous insulin readily restores normal blood glucose level.

2.Streptozotocin (Szkudelski T 2001)

Streptozotocin [STZ, 2-deoxy-2-{3-(methyl-3-nitrosoureido)-D-glucopyranose}] is synthesized by streptomycetes achromogenes and is used to induce both Type-1 and Type-2. It is freely soluble in water, unstable at room temperature and has to be stored below -20 °C. Streptozotocin induces diabetes in almost all the species. Diabetes dose varies with the species and the optimal dose required to produce diabetes in rat was found to be (50 – 60 mg/kg i.p. or i.v.), in mice (175-200 mg/kg i.p. or i.v.) and in dogs (15 mg/kg, for 3 days). Due to its low stability the rapid i.v. injection appears to be the best route of administration. STZ induces diabetes in hamster, monkey and guinea pigs. STZ diabetes can be induced by two ways either by single injection of STZ or by multiple low dose injection of STZ. Like alloxan, it shows triphasic fluctuation pattern in diabetes. Initial hyperglycemia is observed by 1 h after the injection followed by hyperglycemia and again a hyperglycemia state at 48 h, the elevated blood glucose level is observed by 48-72 h (peak effect) and is maintained

thereafter. Different mechanisms of action on the β-cells destruction by STZ have been proposed. Its main actions is through free redical generations. Other report proposed that STZ exerts lethal damage by alkylting DNA or its phosphate backbone as well as glycolytic or mitochondria enzyme. STZ also influence the immune system by suppressing the T-cell function associated with atrophy of the thymus and peripheral lymphoid tissue. Like alloxan, STZ also induces OFR induced lipid peroxidation and DNA strand breaking in pancreatic islet cell. Streptozotocin enters the β-cell via a glucose transporter (GLUT 2) and cause alkylation of DNA. DNA damage induces activation of poly ADP-ribosylation leads to depletion of cellular NAD^+ and ATP. Enhanced ATP dephosphorylation after streptozotocin treatment supplies a substrate for xanthine oxidase resulting in the formation of superoxide radicals. Consequently, hydrogen peroxide and hydroxyl radicals are also generated. Furthermore, streptozotocin liberates toxic amounts of nitric oxide that inhibits aconitase activity and participates in DNA damage

Other diabetogenic agents

1. Dehydroascorbic acid 650 mg/kg for three days in rat
2. Dehydroisoascorbic acid 1.5 mg/kg in rat
3. Dehydroglucoascorbic acid 3.5-3.9 gm/kg in rat
4. Methyl Alloxan 53 mg/kg in rat
5. Ethyl Alloxan 53-130 mg/kg in rat
6. Oxime & Dithizone 53 mg/kg in rabbit
7. Sodium Diethyldithiocarbonate 0.5-1 gm/kg in rabbit
8. Potassium Xanthate 200-350 mg/kg in rabbit
9. Uric Acid 1 gm/kg in rabbit

The Herbal Solution for Insulin Resistance

In the 1980s Chinese doctors became alarmed by reports of sharp increases in the incidence of obesity, diabetes, heart disease and breast cancer. Noting that the conditions were linked with the relatively recent increase in Chinese citizens adopting Western eating habits, leading Chinese doctors began to prescribe a number of modern Western drugs to treat the disorders. Soon, though, a number of medical

experts expressed concern that, in addition to presenting serious side effects, the drugs were failing to address the root of the problem, namely the underlying disruption of normal metabolic processing and energy production.

The most important therapeutic principle in Chinese medicine is to treat both acute symptoms and the cause of a problem at the same time. Based on this principle, Chinese researchers turned to traditional herbs that were well studied and widely used for diabetes. After almost ten years of clinical evaluation a team of doctors at Shanghai People's Hospital introduced a unique herbal blend that effectively countered insulin resistance, lowered blood sugar levels and restored healthy pancreatic function.

In clinical tests the herbal ingredients were also shown to restore health by countering the wide range of disorders that accompany diabetes, such as cardiovascular disease, degenerative eye conditions, skin ulcerations, limb numbness and pain, and kidney dysfunction.

Ingredients of that unique herbal blend include a select group of herbs that have been shown to support recovery from the metabolic disturbances common to metabolic syndrome:

- **Wolfberry** (root bark and fruit) steadily lowers blood sugar to normal levels.
- **Hawthorn** (crataegus) normalizes blood sugar levels while improving cardiovascular function.
- **Curcumin** normalizes blood sugar levels, restores bile production (for better absorption of fats from foods), and inhibits the formation of advanced glycation endproducts (AGEs) that have been implicated in cataract formation, nephropathy and neuropathy in diabetes.
- **Cordyceps** improves insulin resistance to enhance glucose utilization in skeletal muscles and restore basal insulin levels in the pancreas. Cordyceps also aids in reducing serum cholesterol and triglyceride levels.
- **Pumpkin** is widely in China as a health food for diabetics to aid in regulating blood sugar levels.

- **Ophiopogon** promotes healing of the islets of Langerhans and increases glycogen storage. Studies on ophiopogon have shown it aids in lowering blood sugar levels, reducing inflammation and protecting against bacterial infection.

In a placebo controlled experiment on the effect of polyherbal formulation, Yu Xiao San 8805(containing *Euonymus alatus, Cortex Lycii Radicis, Arctium Lappa L, Platycodon Grandiflorum, Litchi Chinensis, Curcuma longa, Panax quinquefolium* L.) on the treatment of hyperglycemia using a streptozotocin-induced insulin resistant diabetic rat model. Dr. Ida Chen, stated that Yu Xiao San 8805 has shown statistically significant effect on the increase in triglycerides (TG) in streptozotocin-induced insulin resistant diabetic rats.

Plants Used In Insulin Resistance

Plant	Part Used	Family	Mechanism
Brassica Juncea(Rai) (Yadav SP et al 2004)	Seeds	Brassicaceae	Its antioxidant activity is responsible for its action.
Momordica Charantia (Vats et al 2001)	Fruit	Cucurbitaceae	Act by countering the impairment of insulin action in skeletal muscle and liver.
Eugenia Jambolana (Vats et al 2001)	Kernels		Act by countering the impairment of insulin action in skeletal muscle and Liver.
Cinnamon (Qin B et al 2004)	Bark	Lauraceae	By enhancing insulin signaling Via. the "NO" pathway in skeletal muscle.
Acanthopanax Senticosus (Tsang-Pai-et al 2001)	Root	Araliaceae	By improving insulin sensitivity
Panax Ginseng (Liu TP et al 2005)	Root	Araliaceae	By improving insulin sensitivity
Pterocarpus Marsupium(Vijayasar) (JK Grover et al 2005)	Bark	Leguminosae	Not know
Polygonatum odoratum(Mill.) Druce. (Choi SB & Park S 2002)			By promoting peripheral insulin sensitivity.
Stevia Rebaudiana (Yajima H et al., 2004)			Increases skeletal muscle glucose transport system.

Antihyperlipidemic Treatment

There are several herbs and supplements that appear to help lower cholesterol levels. Stanols are substances that occur naturally in various plants. Plant stanol esters reduce serum cholesterol levels by inhibiting cholesterol absorption (Tammi A et al., 2000). Numerous double-blind, placebo-controlled studies, ranging in length from 30 days to 12 months, have found stanol esters and their chemical relatives effective for improving cholesterol levels(Gylling H et al., 1994;1999; Vanhanen HT et al., 1993).The combined results suggest that these substances can reduce total cholesterol and LDL ("bad") cholesterol by about 10%-15%(Nguyen TT 1999). Stanol esters did not have any significant effect on HDL ("good") cholesterol or triglycerides in most of these studies. Water-soluble fiber supplements appear to lower cholesterol, (Yokoyama M et al., 2007) and the FDA has permitted products containing this form of fiber to carry a "heart-healthy" label (Glore SR et al., 1994). Soy protein appears to lower total cholesterol by about 9%, LDL ("bad") cholesterol by 13%, and triglycerides by 10%.(Anderson JW et al., 1995; Reynolds K et al., 2006) In a double-blind, placebo-controlled study of 143 individuals with elevated cholesterol, artichoke leaf extract significantly improved cholesterol readings. (Englisch W et al., 2000) Total cholesterol fell by 18.5% as compared to 8.6% in the placebo group; LDL cholesterol fell by 23% versus 6%; and the LDL to HDL ratio decreased by 20% versus 7%. Artichoke leaf may work by interfering with cholesterol synthesis (Petrowicz O et al., 1997). A compound in artichoke called luteolin may play a role in reducing cholesterol (Kraft K 1997). One double-blind study found evidence that cinnamon, taken at a dose of 1-6 grams daily, improved triglyceride, LDL cholesterol, and total cholesterol, without worsening HDL-cholesterol.(Khan A et al., 2003).Inconsistent evidence hints that flaxseeds might reduce LDL cholesterol and, overall, slow down atherosclerosis.(Prasad K 1997; Arjmandi BH et al.,1998), Other preliminary double-blind trials suggest potential benefit with the Iranian herb *Achillea wilhelmsii*,(Asgary S et al., 2000) the Peruvian herb Caigua (*Cyclanterha pedata*), carob fiber,(Gonzales GF et al., 1995; Zunft HJet al., 2003) the Chinese caterpillar/fungus cordyceps,(Shao Get al., 1990) *Ipomoea batatus* (sweet potato),(Ludvik BH et al., 2002) and a drink containing broccoli and cabbage.(Takai Met al., 2003) A number of studies published in the 1980s and 1990s reported that various

garlic preparations, including raw garlic, stabilized garlic powder, and aged garlic, can lower cholesterol.(Temme EH et al., 2002; Amundsen AL et al., 2002) Guggul, the sticky gum resin from the mukul myrrh tree, has been widely marketed as a cholesterol-reducing herb.

Chitosan, a type of insoluble fiber derived from crustacean shells, has been proposed for reducing cholesterol levels, but current evidence suggests that if it does offer any benefits, they are minimal at best(Maezaki Yet al., 1993). Weaker, and in some cases inconsistent, evidence suggests potential benefit with berberine (found in goldenseal, honey, Oregon grape, and barberry),(Anderson JW, Gilliland SE 1999) grape polyphenols,(Zern TL et al., 2005) alfalfa,(Story JA et al., 1984) beta-hydroxy-beta-methylbutyrate (HMB),(Nissen S et al., 2000) CLA (CLA),(Noone EJ et al., 2002) L-carnitine,(Davini P et al., 1992) mesoglycan,(Vecchio F et al.,1993) and blue-green algae.(Iwata K et al., 1990).

Antihyperlipidemic Plants

Plant	Family	Organ	Mechanism
Coriandrum Sativum (A Arun Sam Lal et al., 2004)	Umbelliferae	Leaves, Seeds	Act by decreasing uptake & by enhancing the breakdown of lipid
Trichila Connaroids (AL Purnima et al., 2003)	Meliaceae	Leaves	By interfering with cholesterol biosynthesis.
Curcuma Longa (VP Dixit et al.,1988)	Zinziberaceae	Tuber	By increasing serum CHOL catabolism.
Nardostachys Jatamansi (VP Dixit et al., 1988)	Valerianaceae	Whole Plant	By increasing serum CHOL catabolism.
Achyranthus Aspera (AK Khanna et al., 1992)		Aerial Parts	By rapid excretion of bile acids causing low absorption of CHOL.
Cassia Tora (Umesh K,et al., 2004)	Caesalpiniaceae	Seeds	By inhibiting fatty acetyl-CoA activity & glycerophosphate acetyl transferase.
Phaseolus Aconitifolius (M Mayilvaganan et al., 2004)		Seeds	By increasing LDL catabolism or by reducing LDL synthesis
Adenocalymma Alliaceum (MR Srinivasan & K Srinivasan 1995)	Bignoniaceae	Flower	Act by decreasing intestinal cholesterol absorption
Allium Sativum (CG Sheela and KT Augusti 1995)	Liliaceae	Bulbs	By enhancing CHOL degradation
Enicostemma Littorale Vihas T et al., 2005)	Gentianaceae	Whole Plant	By inhibiting HMGCoA reductase activity
Pterocarpus marsupium (Jahromi MA et al., 1993)		Heart wood	Not know
Trigonella foenum graecum (M Prasanna 2000)		seeds	Not know
Phyllanthus niruri (AK Khanna et al., 2002)	Euphorbiaceae	Whole plant	By enhancing LCAT activity.
Paeonia lactiflora, (Hyun Yang et al., 2004)	Ranunculaceae	Roots	Not know
Glycine tomentella (Ko YJ et al., 2004)	Leguminosae	root	Not know

Animal models for experimental Hyperlipidemia & Atherosclerosis

- **Experimental Atherosclerosis**
  - Cholesterol-diet induced atherosclerosis in rabbits and other species
  - Hereditary hypercholesterolemia in rats
  - Hereditary hyperlipidemia in rabbits
  - Transgenic animals
  - Evaluation of endothelial function in rabbits with atherosclerosis
  - Intimal reactions after endothelial injury
- **Influence on lipid metabolism**
  - Hypolipidemic activity in rats
  - Hypolipidemic activity in Syrian hamsters
  - Triton-induced hyperlipidemia in rats
  - Fructose induced hypertriglyceridemia in rats
  - Intravenous lipid tolerance testin rats
  - Influence on lipoproteinlipaseactivity
  - Influence on several steps of cholesterol absorptionand formation
- **Inhibition of cholesterol biosynthesis**
  - Determination of HMG-CoAreductase inhibitory activity
  - Inhibition of the isolated enzyme HMG-CoA-reductase *in vitro*
  - Inhibition of the incorporation of 14C-sodium acetate into cholesterol in isolated liver cells
  - *Ex vivo* inhibition of cholesterol biosynthesis in isolated rat liver slices
  - Effect of HMG-CoA-reductase inhibitors *in vivo*
- **Inhibition of cholesterol absorption 1118**
  - Inhibition of ACAT (Acyl coenzyme A: cholesterol acyltransferase)
  - *In vitro* ACAT inhibitory activity
  - *In vivo* tests for ACAT inhibitory activity
  - Lymph fistula model for cholesterol absorption
- **Interruption of bile acid recirculation**
  - Cholestyramine binding
- **Inhibition of lipid oxidation**
  - Inhibition of lipid peroxidation of isolated plasma low density lipoproteins
  - Internalization of labeled LDL into HepG2 cells

Experimental atherosclerosis

Experimental atherosclerosis was first successfully induced in rabbits by Saltykow (1908) and Ignatowski (1909). During the following years, various scientists found that dietary cholesterol was the responsible stimulus for development of atherosclerosis. Other species are also susceptible to diet-induced atherosclerosis (Reviews by Kritchevsky 1964; Hadjiinky et al. 1991). A unifying hypothesis of the pathogenesis of atherosclerosis has been proposed by Schwartz et al. (1991).

Cholesterol-diet induced atherosclerosis in rabbits and other species:

Rabbits are known to be susceptible to hypercholesterolemia and arteriosclerosis after excessive cholesterol feeding. Therefore, this approach has been chosen by many authors to study the effect of potential anti-arteriosclerotic drugs.
Shore and Shore (1976) studied two different strains of rabbits (New Zealand White and Dutch Belt) as models of hyperlipoproteinemia and atherosclerosis.
In rats hypercholesterolemia can be induced by daily administration by gavage of 1 ml/100 g body weight of a cocktail containing in 1 l peanut oil: 100 g cholesterol, 30 g propylthio-uracil, and 100 g cholic acid over a period of 7 days. The test compounds are
administered simultaneously with the cocktail (Fillios et al. 1956; Lustalot et al. 1961).
Diet-induced hypercholesterolemia is useful only for detection of agents interfering with the adsorption, degradation and excretion of cholesterol. Agents interfering with cholesterol biosynthesis are less probable to be detected.

Influence on lipid metabolism

Elevated lipid levels, especially hypercholesterolemia, result from increased absorption from the gut or enhanced endogenous synthesis. Therefore, two ways are feasible to reduce hyperlipidemia: to block endogenous synthesis or to decrease absorption. Both factors can be evaluated in normal animals without artificial diets. Clinically used lipid lowering compounds like fibrates can be tested in this way, being investigated with additional tests. Earlier attempts to interfere with endogenous cholesterol synthesis resulted in accumulation of other sterols than cholesterol (Holmes 1964).The most extensively studied approach to inhibit cholesterol

biosynthesis is with HMG-CoA reductase inhibitors.Inhibition of other enzymes of cholesterol biosynthesis, such as lanosterol 14□-methyl demethylase, and squalene synthetase, is considered. The inhibition of cholesterol absorption by ACAT-inhibitors is a widely followed approach. Furthermore, the interruption of bile acid recirculation resulting in reduction of

LDL cholesterol is being used.Protective effects of calcium antagonists against experimental arteriosclerosis acting mainly on other mechanisms than lipid metabolism have been claimed by various authors but the clinical relevance is still questionable (Kjeldsen and Stender 1989; Fronek 1990; Knorr and Kazda 1990; Fleckenstein-Grün et al. 1992).

Hypolipidemic activity in rats

Hyperlipoproteinemia with increased concentrations of cholesterol- and triglyceride-carrying lipoproteins is considered to be the cause of arteriosclerosis with its dual sequelae of thrombosis and infarction. Lipoproteins are divided into 6 major classes: chylomicrons, chylomicron remnants, VLDL (very low density lipoproteins), IDL (intermediate density lipoproteins), LDL (low density lipoproteins), and HDL (high density lipoproteins) HDL promotes the removal of cholesterol from peripheral cells and facilitates its delivery back to the liver. Therefore, increased levels of HDL are desirable. On the contrary, high levels of VLDL and LDL promote arteriosclerosis. LDL, especially in its oxidized form, is taken up by macrophages via a scavenger mechanism. Therefore, anti-arteriosclerotic drugs should reduce VLDL and LDL and/or elevate HDL.

Inhibition of cholesterol biosynthesis

The following steps are involved in cholesterol biosynthesis:

- HMG-CoA synthase (hydroxymethylglutaryl-coenzyme A synthase)
- Forming hydroxymethylglutaryl-CoA from acetyl-CoA and acetoacetyl-CoA
- HMG-CoA reductase (hydroxymethylglutaryl-coenzyme A reductase)
- Forming mevalonic acid from hydroxymethylglutaryl-CoA.

Inhibition of cholesterol synthesis on this step is used at present successfully for therapy

Determination of HMG-CoA-reductase inhibitory activity

More than 70% of the total production of body cholesterol in humans is derived from de novo synthesis. 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is the rate limiting enzyme governing cholesterol biosynthesis and the synthesis of other isoprenoids in mammalian cells (Rodwell et al. 1976).The development of HMG-CoA reductase inhibitors offers an advance in the treatment of hypercholesterolemia by interfering with the crucial step of cholesterol biosynthesis. When inhibiting hepatic HMG-CoA reductase, the inhibitors trigger an increased production of LDL receptors in the liver. As LDL receptor activity increases, more LDL is extracted from the blood and thus the level of circulating LDL-cholesterol is reduced. Pharmacological evaluation of HMGCoA reductase inhibitors is based on studies on the inhibition of the isolated enzyme HMG-CoA –reductase *in vitro*, on the inhibition of the incorporation of 14C sodium acetate into cholesterol in isolated liver cells, and on the effect of HMG-CoA -reductase inhibitors *in vivo*. HMG-CoA reductase activity has a diurnal rhythm in liver and intestine which has to be considered for *in vivo* studies (Shapiro and Rodwell 1969; Shefer et al. 1972).

Specific Botanicals for Hypertension

Hawthorne (Crataegus oxycantha and monogyna): Hawthorne has been used traditionally for cardiovascular disorders in many cultures. It contains a number of active constituents including flavonoids, catechins, triterpene saponins, amines, and oligomeric proanthocyanidins (OPCs). Hawthorne has been shown to exert a mild blood pressure lowering effect (Leuchtgens H 1993; Schussler M et al.,1995) that can take up to four weeks for maximal results. It is believed that the herb dilates coronary blood vessels.(Schussler M et al.,1995) One in vitro study on rat aorta found proanthocyanidins extracted from Hawthorne relaxed vascular tone via endothelium-dependent nitric oxide-mediated relaxation. (Kim SH et al., 2000).

Arjuna Bark (Terminalia arjuna): Terminalia arjuna is a deciduous tree found throughout India. Its bark has been used in Ayurvedic medicine for over three centuries. Terminalia's active constituents include tannins, triterpenoid saponins, flavonoids, gallic acid, ellagic acid, OPCs, phytosterols, calcium, magnesium, zinc, and copper. Several studies have elucidated Terminalia's effects on various cardiac

disorders including congestive heart failure, coronary artery disease, and hypertension. A study on its effects on stable and unstable angina patients found it effective for those with stable angina, with a 50-percent reduction in angina episodes and significant decrease in systolic blood pressure. (Dwivedi S et al., 1994). In a double-blind crossover study, 12 subjects with refractory chronic congestive heart failure (idiopathic dilated cardiomyopathy (n=10); previous myocardial infarction (n=1), or peripartum cardiomyopathy (n=1)), received Terminalia arjuna, at a dose of 500 mg every eight hours, or placebo for two weeks, each treatment protocol separated by a two-week washout period, as an adjuvant to conventional therapy. Clinical, laboratory, and echocardiographic evaluations were carried out at baseline and at the end of therapy. Terminalia, compared to placebo, was associated with improvement in symptoms and signs of heart failure, decrease in echo-left ventricular end diastolic and end systolic volume indices, increase in left ventricular stroke volume index, and increase in left ventricular ejection fractions. A study with similar dosing on primarily post-myocardial infarction angina patients found improvements in cardiac function. Prolonged use resulted in no adverse side effects or signs of renal, hepatic, or hematological abnormalities.

Olive Leaf (Olea africana and Olea europea): The hypotensive action of olive leaf has been studied for two decades (Visioli F et al., 1998). A clinical study of Olea europaea L. aqueous extract was conducted on two groups of hypertensive patients, 12 patients consulting for the first time, and 18 patients on conventional antihypertensive treatment. An aqueous extract was given for three months, after 15 days of placebo supplementation. Researchers noted a statistically significant decrease of blood pressure ($p<0.001$) for all patients, without side effects. (Cherif S et al., 1996). One of olive leaf's mechanisms of action is vasodilation. In an in vitro study a decoction of olive leaf caused relaxation of isolated rat aorta endothelium. The relaxant activity was independent of the integrity of the vascular endothelium. Oleuropeoside was found to be a component responsible for vasodilator activity; however, the researchers felt at least one other principle was either a vasodilator itself or potentiated the relaxant effect of oleuropeoside. (Zarzuelo A et al., 1991).

European Mistletoe (Viscum album:) Its pharmacological effects, including diuretic and hypotensive activity, were studied using an alcohol extract of Japanese and

European mistletoe. Both extracts showed blood pressure lowering effects when administered intravenously and orally to cats. Other researchers have reported similar hypotensive effects of mistletoe in experimental animal studies. (Petkov V 1979).

Yarrow (Achillea wilhelmsii): A double-blind, placebo-controlled trial examined the antihyperlipidemic and antihypertensive effects of Achillea. The researchers randomly selected 120 men and women, aged 40-60 years, and divided them into two groups: (1) moderate hyperlipidemic and (2) hypertensive subjects. Each study group was treated either with an alcohol extract of Achillea or placebo at a dose of 15-20 drops twice daily for six months. Blood pressure and serum lipids were measured at the end of two, four, and six months. A significant decrease was observed in diastolic and systolic blood pressure after two and six months, respectively ($p<0.05$). (Asgary S et al., 2000).

Black Cumin Seeds (Nigella sativa): Nigella sativa (Ranunculaceae) has a long history of use in folk medicine as a diuretic and hypotensive agent. In an animal study, an oral dose of either Nigella sativa extract (0.6 mL/kg/day) or furosemide (5 mg/ kg/day) significantly increased diuresis by 16- and 30 percent, respectively, after 15 days of treatment. In the same rat study, a comparison between Nigella sativa and nifedipine found mean arterial pressure decreased by 22-and 18 percent in the Nigella sativa and nifedipine treated rats, respectively. (Zaoui A et al., 2000). An animal study found the volatile oil has the potential of being a potent, centrally acting antihypertensive agent. (Tahir KE et al., 1993).

Forskolin (Coleus forskohlii): Coleus forskohlii has been used in Ayurvedic medicine for many years. Forskolin's blood pressure lowering effects appear to be due to relaxation of arterial vascular smooth muscle. In a study with isolated heart tissue, forskolin activated membrane-bound adenylatecyclase and cytoplasmic cAMP-dependent protein kinase. The researchers postulated the positive inotropic effect was via an enhanced calcium uptake by the heart muscle cell. (Metzger H & Lindner E 1981) Another constituent from Coleus, ditermene coleonol, has been found to lower blood pressure in both rat and cat models. (Dubey MP et al., 1981).

Indian Snakeroot (Rauwolfia serpentina): Rauwolfia is cultivated for the medicinal use of its 30 alkaloids (particularly reserpine found in the root), many used in treating hypertension. (Duke JA 1985) In a controlled intervention trial, 389 subjects, ages 21-55 years, with diastolic blood pressures 90-115 mm Hg were examined for 7-10 years. Subjects were randomly assigned to either a combination of a diuretic and Rauwolfia serpentina, or an identical placebo. Diastolic blood pressure was reduced an average of 10 mm Hg and systolic by 16 mm Hg in the active treatment group, with no change in the placebo group. (Smith WM. 1977).The Rauwolfia constituent ajmaline not only lowers blood pressure, but also has a potent antiarrhythmic effect. Studies have shown that ajmaline specifically depresses intraventricular conduction, suggesting this would be particularly effective in the treatment of re-entrant ventricular arrhythmias. (Obayashi K et al., 1976; Kostin IV et al., 1990).

Garlic (Allium sativum): The blood pressure effect is thought to be due to an opening of (Ca) ion channels in the membrane of vascular smooth muscle, affecting hyperpolarization, resulting in vasodilatation. (Siegel G et al., 1999) A garlic preparation containing 1.3-percent allicin at a large dose (2400 mg) was evaluated in an open-label study in nine severely hypertensive patients (diastolic blood pressure 115 mm Hg or greater). Approximately five hours after taking the garlic, the systolic blood pressure decreased an average of 7 mm Hg while diastolic BP dropped an average of 16 mm Hg. A significant decrease in diastolic blood pressure lasted from 5-14 hours after the dose and no significant side effects were reported. (McMahon FG & Vargas R 1993).

Antihypertensive Drugs screening

Screening of drugs with potential cardiovascular activity covers a wide spectrum of pharmacological actions. The various models available for these investigations entail the use of intact animals and isolated organs. Some of these models do not resemble actual clinical situations, yet they have helped to uncover different types of cardiovascular agents with therapeutic applications. Although a large number of drugs are clinically available for the management of hypertension, most of these are either ineffective or their use is often associated with serious side effects. Hence the search continues for agents that are more effective and potent with fewer side effects.

Some of the Screening methods are as follows:

- Hemodynamic screening in anesthetized rats
- Blood pressure in pithed rats
- Antihypertensive vasodilator activity in ganglion-blocked,angiotensin II supported rats
- Blood pressure in conscious rats (tail cuff method)
- Direct measurement of blood pressure in conscious rats with indwelling catheter
- Cannulation techniques in rodents
    - Permanent cannulation of the jugular vein in rats
    - Permanent cannulation of the renal vein in rats
    - Permanent cannulation of the portal vein in rats
    - Permanent cannulation of the thoracic duct in rats
- Cardiovascular analysis in anesthetized mice
- Blood pressure in anesthetized cats
- Cardiovascular drug challenging experiments in anesthetized dogs
- Hemodynamic analysis in anaesthetized dogs
- Hemodynamic measurements in conscious dogs
- Hemodynamic studies in monkeys
- Measurement of cardiac output and its distribution with microspheres
    - Carotid artery loop technique
    - Measurement of heart dimensions in anesthetized dogs
    - Telemetric monitoring of cardio-vascular parameters
- Cardiovascular effects after intracerebroventricular administration
- Influence on orthostatic hypotension
- Bezold-Jarisch reflex
- Heat stroke
- Alpha adrenoreceptors in the mouse iris
- Alpha 2 adrenoceptor blockade measured *in vivo* by clonidineinduced sleep in chicks
- Activity at Alpha 1 and Alpha 2 adrenoreceptors in the rat
- Alpha 1 and Alpha 2 sympatholytic activity in dogs
- Intrinsic sympathomimetic activity in reserpine-pretreated dogs

- Cat nictitating membrane preparation (ganglionic blocking activity)
- Assessment of ganglion-blocking activity in the isolated bovine retractor penis muscle
- Angiotensin II antagonism
- ACE inhibition measured *in vivo* in the rat
- Evaluation of renin inhibitors in dogs
- Evaluation of renin inhibitors in monkeys

Possible Mechanisms of Antifertility

Specific hormonal equilibrium of estrogen and progesterone is required for blastocyte implantation. So any imbalance of these hormones causes termination of pregnancy.

1) **Antiestrogenic activity:** Antiestrogenic activity causes degeneration of oocytes. It causes various biochemical changes in the uterus. The biochemical constituents such as glycogen, protein and the activity of acid phosphatase decreases on the day of implantation. The uterus also shows unresponsive changes such as lack of leucocytic infiltration, apposition reaction and decidual response.
2) **Progestational activity:** Increase in the level of progegterone level causes imbalance in the equilibrium of estrogen-progesterone and causes the interruption of pregnancy.
3) **Antiprogestational activity:** Administration of an antiprogestrtional drug during pregnancy results in the withdrawal of progesterone support to the endometrium, menstrual bleeding, and the disruption of placental function. Antiprogestins also stimulate the secretion of prostaglandins and reduce its metabolism. Myometrial contractile activity is normally regulated by the balance between the inhibitory action of progesterone and the stimulatory action of prostaglandin. During pregnancy, myometrial activity is suppressed: during labour, the production of prostaglandins increases and myometrial contractility increases. Hence the increase in prostaglandin level aids in abortifacient action.
4) **PGF and its analogs:** A PGF-induced luteolysis causes a decline in progesterone, withdrawal of progesterone action and as a result, termination

of pregnancy. Prostaglandin is also a utero-tonic and the uterine contractions caused by PGF facilitate its abortifacient action.

5) **Dopamine agonists:** Dopamine agonists and related compounds suppress prolactin secretion. Prolactin is a required luteotrophin in pregnancy. Dopamine agonist administration causes a suppression of prolactin secretion and thus results in luteolysis and termination of pregnancy due to progesterone withdrawal.

Review of Plants with Antifertility Activity

Ayurvedic medicine from the Indian sub-continent is suggesting important leads for researchers in the field of antifertility. Ancient Indian literature abounds with information on large numbers of plants reputed to have sterilizing, contraceptive and abortifacient properties. Scholars of Ayurveda have also mentioned several plants in their Ayurvedic treatises. A number of these preparations are still being used by Ayurvedic physicians all over India.

Hibiscus rosa sinensis: In herbal remedy with an ancient history is currently receiving attention as a potential tool in population control. Hibiscus rosa sinensis is a common ornamental plant cultivated widely throughout India and Burma. Flowers of this plant are said to possess anti-fertility property by ancient Ayurvedic texts. Traditional use of the flowers in Kerala (Southern India) is for its emmenagogue and contraceptive action.

H. rosa sinensis flowers possess significant antifertility activity with the effects dependant upon the dose, duration of the treatment and the stage of the pregnancy. The presence of potent anti-estrogenic activity in the flower portion may be the responsible factor in terminating pregnancy.

An antifertility agent can work by any one or combination of factors. These can include, rapid expulsion of the fertilized ova from the fallopian tube or by the tube locking mechanism; as a blastocyst-toxic agent; by the inhibition of implantation due to a disturbance in estrogen-progesterone balance; or through foetal absorption or abortion, perhaps due to lack of supply of nutrients to the uterus and thus to the embryo.

Not only does H. rosa sinensis have an impact on female reproduction but also on that of males. Extracts of the flowers also affect the generation of sperm

as well as the endocrine function of the testes themselves. The herb's effect upon the male reproductive system has been studied in rats by observation of changes in weight, histology and endocrine functions.Though effective in affecting spermatogenesis the use of H rosa sinensis as a male contraceptive is unlikely due to probable reduction of libido because it suppresses endocrine activity of the testis. Although, the effects are reversible, persistent daily therapy would be needed because of the rapidity by which pituitary function could recover. Such a herbal remedy having a potent antifertility activity in women and reversible anti-spermatogenic effect in men offers the potential of a safe and acceptable aid in the drive to controlling population growth.

Malvaviscus conzattii: The Malvacaea family contains other potential anti-fertility plants. Malvaviscus conzattii is another Indian ornamental plant whose flower closely resembles that of Hibiscus rosa sinensis. There is a marked anti-spermatogenic activity in the flowers of Malvaviscus conzattii. In more animal experiments the testes were damaged and a reduction in male sex hormones production was reflected by the atrophy of the accessory organs. Along with atrophy of the gonadal glands, a significant reduction in levels of protein and sialic acid of testes, epididymis and seminal vesicles was also recorded, since protein anabolism is dependent on androgenic production and also sialic acid and protein contents of the sex accessories reflect changes in testicular androgen production. The genital degenerative changes were found to be more pronounced when the results were observed after oral administration of 50 doses. The drug administration resulted in mass atrophy of the spermatogenetic elements and the testicular stages were left with only 1-2 cell layers. Changes in testicular cholesterol level are physiologically important as cholesterol is involved in spermatogenesis and is responsible for androgen synthesis. In the study of the herbs impact on the treated animals, tissue changes paralleled increased cholesterol level in the testes.

Embelia ribes: Dried berries of another Indian herb, Embelia ribes, have a tradition reputation for an anti-fertility activity. One of its active components, embelin has been documented to possess significant anti-implantation activity in rats but its hormonal activity is still controversial. Studies show that embelin is a potent oral contraceptive of plant origin which possesses 85.71% anti-implantation activity in rats when administered at 50 mg/kg for 7 days and

also inhibits pregnancy at single dose regimen. Embelin inhibited pregnancy and also possesses anti-estrogenic and weak progestational activity. From this it is possible that administration of embelin may cause a disturbance in the hormonal levels and thus prevent implantation, since specific hormonal equilibrium of estrogen and progesterone is required for egg implantation. Another suggestion is that it produces a change in the uterine environment which inhibits or interferes in the process of implantation. It may also have a direct action on the hypothalamus and releasing factors, interfering thereby with the secretion of gonadotropins.

Plants with Antifertility activity

Rivea hypocrateriforms (Shivalingappa H et al., 2002)	Salvia fruticosa (Al-Hamood MH et al., 1998)	Carica papaya Linn (Garg SK & Garg GP.1971)
Pueraria tuberose (Prakash AO et al., 1987)	Plumbago zeylanica (Premakumari P et al., 1977)	Daucus carota Linn (Garg SK & Garg GP.1971)
Plumbago rosea (Sarma HN et al., 2002)	Striga densiflora (Shivayogi P. Hiremath et al., 1996)	Grewia asiatica Linn (Garg SK & Garg GP.1971)
Borassers habellifer (Sarma HN et al., 2002)	Derries brevipes (Shrishailappa Badmi et al., 2003)	Taxus baccata Linn (Garg SK 1972)
Carica papaya(male) (Sarma HN et al., 2002)	Embeila ribes (Kholkute SD et al., 1978)	Polygonum hydropiper Linn (Vohora SB et al., 1969)
Dolichos lablab (Sarma HN et al., 2002)	Moringa oleifera (Shukla S 1988)	Crotolaria juncea Linn (Rao VS et al., 1979)
Shorea robusta (Sarma HN et al., 2002)	Lygodium flexosum (Gaitonde BB et al., 1980)	Annona squamosa Linn (Rao VS et al., 1979)
Calotopis procera (Circosta C et al., 2001)	Mentha arvensis (Bodhankar SL et al 1974)	Curcuta reflexa Roxb (Rao VS et al., 1979)
Pueraria tuberose (Sangeeta shulkaet al., 1996)	Momordica angustisepala (Aguwa CN et al., 1983)	Cuminum cyminum Linn (Garg SK 1976)
Illicium anisatum (Dhar SK 1995)	Momordica chartina	Hyptis suaveolens Poit

Ocimum sanctum (Batta SK et al., 1971)	(Saksena SK et al., 1971)	(Garg SK 1976)
Hibiscus rosa sinensis (Batta SK et al., 1971)	Momordica dioxica (Sreedhar CS 2002)	Butea frondosa (Suganthan D et al., 1979)
Areca Catechu (Garg SK & Garg GP.1971)	Spondias mombin Linn (Offiah VN 1989)	Ailanthus excelsa (Dhanasekaran S. et al., 1993)
Nigella sativa (Keshri G et al., 1995)	Jatropha curcas (Goonaekera MM et al., 1995)	Achrostichum aureum (Dhar JD et al., 1992)
Striga orobancteroides (Hiremath SP et al., 2000)	Crotalaria spectabilis (Rosane Maria T et al., 2000)	Striga lutea (Hiremath SP et al., 1990)
Coriandrum sativm (Al-Said MS et al., 1987)	Coleus barbatus B (Feranada CG et al., 2000)	Taxus baccata Linn (Khanna U et al., 1969)
Citrus hystrix DC (Piyachaturawat P et al., 1985)	Sida veronicaefolia (Lutterodt GD 1988)	Urarialagipoides DC (Khanna U et al., 1969)
Calotropis procera (Kamath VJ et al., 2000)	Azairachta indica (Prakash AO et al., 1988)	Rivea hypocrateriformis (Shivalingappa H et al., 2001)
Acalpha indica. L (Hiremath SP et al., 1999)	Inula viscose (Nisreen M. Al-Dissi et al., 2001)	Azadirachta indica (Mukherjee S et al., 1999)
Adhota vasica (Nath D et al., 1992)	Piper longum (Garg SK 2001)	Cajanus cajan (L) millps (Lemonica IP 1994)
Acanthospermum hispidium DC (Lemonica IP 1994)		Moringa oleifera (Nath D et al., 1992)

Natural Antioxidants in Herbs

The body of knowledge about plants, herbs and spices and their respective and collective roles in promoting human health is modest. Dietary compounds, their role in maintaining human health and their interactions with established nutrients need to be determined to be research priorities. A number of fruits and vegetables have been shown to actually combat the deleterious effects of metabolic oxidation generated naturally or by increasing pollutants in the environment.

The plants that show good antioxidant activity include Allium cepa (Onion), Allium sativum (Garlic), Aloe camells (Sinensis) (Green tea), Curcuma longa (Turmeric), Emblica officinalis (Amla), Glycyrrhiza glabra (Licorice), Hemidesmus indicus (Anantamul), Mangifera indica (Mango), Ocimum sanctum (Tulsi), Picrorhiza kurroa (Katuka), Tinosporacordifolia (Guduchi), Withania somnifera (Ashwagandha) and Zingiber officinale (Ginger) . There are still a large number of plants and ayurvedic formulations whose antioxidant activities need to be examined in relation to their potential therapeutic and related beneficial properties.

According to recent studies, antioxidants vitamins in various products and other foods may actually represent a modern day "Fountain of Youth". In effort to beef up bodily defenses to combat free radical activity, scientists are studying the effects of increasing individual's antioxidant levels through diet and dietary supplements. A large number of compounds from various plant sources have been shown to possess antioxidant properties. Antioxidants of plants origin are vitamin E and C, selenium, phenolic compounds, carotenoids, flavonoids etc. It has been assumed that nutritional intervention to increase intake of phytoantioxidants may reduce threat of free radicals.

Mentha extract have shown to have antioxidant and antiperoxidant properties due to the presence of eugenol, caffeic acid, rosmarinic acid and Alpha-tocopherol. The aqueous extract has also been screened for antibacterial activity against Pseudomonas solanacearum . Antifungal activity of peppermint oil against Aspergillus niger, Alternaria alternata and Fusarium chlamydosporum has also been claimed.

Cucurmin, containing a double bond in conjugation with phenyl ring is, a powerful radical scavenger. The feluric acid present in plants, due to its phenolic nucleus and an extended side chain conjugation, readily forms a resonance stabilized phenoxyl radical which accounts for its potent antioxidant potential. Isoeugenol, which has a conjugated double bond, is good radical scavenger. The double bond in conjugation with the phenyl ring plays an important role in the antioxidant activity of this compound. Polyphenolic flavonoids inhibit lipid peroxidation by forming less reactive aryloxyl radicals with free radicals. Rutin was capable of modifying membrane dependent processes such as free redical induced membrane lipid peroxidation. Plant flavonoids which show antioxidant activity in vitro also function as antioxidants in vivo, and their radioprotective effect may be attributed to their radical scavenging activity.

Rasayans is a group of drug prepration used in Ayurvedic system of medicine to improve the health of body. The oral administration of Rasayans protected mice from radiationinduced leucopenia and reduced the formation of lipid peroxidase in liver as compared to controls. Pre-treatment of some antioxidants like curcumin, bixin, ellagic acid and alpha-tocopherol before exposure to gamma rays, significantly declined the serum and lipid peroxidase enzymes. Liv.52 (a non-toxic herbal prepration) has been reported to be clinically effective in treating hepato-toxicity and wide range of hepatic disorders of different etiology. Its hepato-protective role against irradiation and/or methylmercuric chloride (MMC) intoxication has also been demonstrated.

Aim of the Present Study:

Momordica charantia is the only species in Momordica genus that has been frequently used as medicine (Giron et al., 1991; Lans and Brown, 1998). In the last few decades several hundred studies that have been carried with *Momordica charantia*, using modern tools, credit it with antidiabetic, antiviral, antitumor, antileukemic, antibacterial, anthelmintic, antimutagenic, antimycobacterial, antioxidant, antiulcer, anti-inflammatory, hypocholesterolemic,hypotriglyceridemic, hypotensive, immunostimulant, and insecticidal properties (Ng et al., 1992; Raman and Lau, 1996; Basch et al., 2003). *Momordica charantia*, contains biologically active chemicals, several phytochemicals such as momorcharins, momordenol,momordicilin, momordicins, momordicinin, momordin,momordolol, charantin, charine, cryptoxanthin,cucurbitins, cucurbitacins, cucurbitanes, cycloartenols, diosgenin,elaeostearic acids, erythrodiol, galacturonic acids, gentisic acid, goyaglycosides, goyasaponins, multiflorenol, etc (Husain et al., 1994; Xie et al., 1998;Yuan et al., 1999; Parkash et al., 2002). These are reported in all parts of the plant (Murakami et al., 2001). *Momordica charantia* is one of the most commonly prescribed antidiabetic plants

Momordica cymbalaria (MC) being one of the plants in Momordica genera has not been studied extensively for its pharmacological properties. One of the reasons may be it is a seasonal plant, growing in limited geographical regions. But the traditional medical Practitioner (Aurveda and other forms of practices) claim that MC has a better antifertility activity than *Momordica charantia* .It has been claimed by the folklore medicine for use in diabetes mellitus and other metabolic disorders.

Momordica dioica (MD) is a more commonly available vegetable and is used as household antidiabetic medicine and it has not been experimentally explored.

Therefore in the present study a detailed investigation in undertaken on *Momordica cymbalaria* and *Momordica dioica* for various pharmacological activities in

- ⇒ **Metabolic Disorder**
- ⇒ **Cardiovascular Disorder**
- ⇒ **Antioxidant Parameters**
- ⇒ **Reproductive Parameters**
- ⇒ **Isolated Tissues**

Saponins from these plants were isolated, obtained their HPTLC fingerprinting and studied for the following pharmacological activities as follows

- ⇒ **Metabolic Disorder**
- ⇒ **Cardiovascular Disorder**
- ⇒ **Isolated Tissues**