1 INTRODUCTION

1.1 HERBAL MEDICINE

The human body is a rare gift of God. It is our foremost duty to maintain good health and cure the disease if any. A retrospection of the healing power of plant is absolute need of the hour. Herbal medicine is based upon the premise that plants contain natural substances that can promote health and alleviate illness with minimum side effects. Synthetic drugs are not only expensive but many of them bring about serious side effects and toxicities which are sometimes more dangerous diseases themselves. Herbal drugs have great growth potential in the global market. Natural product research continues to explore Indian Traditional Medicines to develop new and novel drugs. Although, most of the countries have made specific rules for the quality control and standardization of herbal drugs there is a need to establish them. In this regard we have large folkloric ancestral assistance by means of Ayurveda and local Vaidyas those practicing traditional medicine till today. [1]

The World Health Organization (WHO) has estimated that 80% people of earth’s 6 billion inhabitants rely upon traditional medicines for their primary health needs and a major part of this therapy involve the use of plant extracts or their active principles. Scientists in many parts of the world have carried out extensive research have proved to humanity the effectiveness and use of herbal medicine. Ayurveda, the traditional medicine practice of India have been recognized to have convincing and credible healing powers. [2]

India has a rich heritage of traditional medicine constituting with its different components like Ayurveda, Siddha and Unani. It is one of the largest producers of medicinal herbs and is rightly called “Botanical Garden of the World”. There are few herbs having medicinal properties and widely used by the population but not yet scientifically documented. Medicinal herbs have been used in India for thousands of years, in one form or the other, under the indigenous system of medicine like Ayurveda, Sidha and Unani. India is all set for herbal medicinal marketing worth Rs. 6000 crores during next five years and may become a global supplier of herbal
product confirming to International standards. Leading Indian research centers have started to produce patentable gene using latest genetic engineering techniques. India is one of the world’s twelve leading biodiversity centers with the presence of 45,000 different plant species, out of which about 15,000-20,000 plants have good medicinal values. However, traditional communities use only about 3,000 plants and modern medicine use only 41 plants for their medicinal importance.\[^2\]

Last few decades have witnessed the use of allopathic drugs to their maximum, but people have become conscious of the adverse effects with usage of these drugs. This has forced the researchers for the search of alternative system of medicine using natural products.

The current interest and demand for herbs is a world wide phenomenon. WHO currently encourages, recommends and promotes herbal or traditional remedies in national health care programmes because such drugs are easily available at low cost and having minimum side effects. They are comparatively safe and the people have faith on such remedies. At present, a substantial portion of global market is represented by plant materials and herbal remedies. From research point of view, natural products are rapidly being utilized as sources of drug discovery and development. In USA over 60% of approved drugs and pre new drug application (NDA) candidates, developed as anticancer and anti-infective agents are of natural origin. The development in the field of plant based drugs are of utmost concern to India, the majority of whose population depends on traditional and indigenous medicines for their primary healthcare needs. Ayurveda, the very foundation of the ancient medical science of India is the backbone of our understanding of plant drugs.\[^3\]

Plants are complex in their composition and their therapeutic efficacy is usually due to several active compounds as well as of inert accompanying substances. The therapeutic constituents are influenced by several factors such as age, geographical location and harvesting period, as concentration of active constituent is not constant throughout the year. In addition, improper authentication of herbs, adulteration and contamination of plants with residue of pesticides, microorganisms, aflatoxins and
heavy metals contribute to the lowering of quality with increased toxicity of their final product. Thus, standardization and quality control of medicinal plants and their formulation is important to ensure the desired therapeutic efficacy.

Herbal medicine also called as botanical medicine or phytomedicine refers to using a plant's seeds, berries, roots, leaves, bark, flowers or whole plant for medicinal purposes. Herbalism has a long tradition of use outside the conventional systems of medicine. It is becoming more main stream because, improvement in analysis and quality control along with advances in clinical research showed the value of herbal medicine in treating and preventing diseases.

Herbal medicine is a practice that is as old as mankind and certainly older than agriculture or writing. Every human culture on each continent of the Earth has practiced herbal medicine in one form or the other. Perhaps best described as "medicinal botany", herbal medicine involves taking plants, ingesting them, and seeing if some of the elements in the plant have a palliative effect on the symptom of the ailment.

Herbal remedies have formed the basis of traditional medicine for millennia and have formed the root of modern pharmacology. While science from 1880's onwards has striven to isolate the active compounds found in medicinal herbs, the list is ever growing.

Among the healing agents isolated from herbal remedies are, salicylic acid (aspirin), derived from white willow bark, the vincristine series of anticancer agents, derived from periwinkle, several stimulants such as ephedra and cocaine and several analgesics and paralytics such as morphine, a tincture from the Opium poppy.

As medical science has delved into molecular biology, and the ways these compounds work has been explored, validation for a number of types of herbal remedies have been found. These include phytochemicals used as anti-oxidants, the benefits of various vitamins for the body.
1.1.1 History of Herbal Medicine

Herbal medicine is the oldest form of healthcare known to mankind. Herbs had been used by all cultures throughout history. It was an integral part of the development of modern civilization. Primitive man observed and appreciated the great diversity of plants available to him. The plants provided food, clothing, shelter, and medicine. Much of the medicinal use of plants seems to have been developed through observations of wild animals, and by trial and error. As time went on, each tribe added the medicinal power of herbs in their area to its knowledgebase. They methodically collected information on herbs and developed well-defined herbal pharmacopoeias. Indeed, well into the 20th century much of the pharmacopoeia of scientific medicine was derived from the herbal lore of native peoples. Many drugs commonly used today are of herbal origin. Indeed, about 25% of the prescription drugs dispensed in the United States contain at least one active ingredient derived from plant material. Some are made from plant extracts; others are synthesized to mimic a natural plant compound.

Undisputedly, the history of herbology is inextricably intertwined with that of modern medicine. Many drugs listed as conventional medications were originally derived from plants. Cinchona bark is the source of malaria-fighting quinine. The *O. poppy* yields morphine, codeine and paregoric, a treatment for diarrhoea. A tincture of the *O. poppy* was also the favored tranquilizer in Victorian times. Even today, morphine is the most important alkaloid of the *O. poppy* remains the standard against which new synthetic pain relievers are standardized.

Prior to the discovery and subsequent synthesis of antibiotics, the herb *echinacea* (which comes from the plant commonly known as *purple cone flower*) was one of the most widely prescribed medicines in the United States. For centuries, herbalists prescribed *echinacea* to fight infection. Today, it has been confirmed that the herb boosts the immune system by stimulating the production of disease-fighting white blood cells.

In 2735 B.C., the Chinese emperor Shen Nong wrote an authoritative treatise on herbs that is still in use today. Shen Nong recommended the use of *Ma Huang* (known as
ephedra in the Western world) against respiratory distress. Ephedrine, extracted from ephedra, is widely used as a decongestant. Its synthetic form, pseudoephedrine is used in many allergy, sinus and cold relief medications produced by large pharmaceutical companies. In China, *herbalism* and herbal remedies were used as an adjunct to acupuncture and the medical morphology in use is of balancing *qui* or *chi*, the life force energies, which have *yin* and *yang* elements. In Chinese *herbalism*, the aim is to bring the systems of the body back into balance by treating it as an electrical system, which is a tactic commonly expressed in modern or *syncretic herbalism*.

The records of King Hammurabi of Babylon (c. 1800 B.C.) include instructions for using medicinal plants. Hammurabi prescribed the use of mint for digestive disorders. Modern research has confirmed that peppermint relieve nausea and vomiting by mildly anesthetizing the lining of the stomach.

The entire Middle East has a rich history of herbal healing. There are texts surviving from the ancient cultures of Mesopotamia, Egypt and India that describe and illustrate the use of many medicinal plant products, including castor oil, linseed oil and white poppies. In the scriptural book of Ezekiel, which dates from the sixth century B.C., we find this admonition regarding plant life and the fruit there of for meat and leaf for medicine. Egyptian hieroglyphs show physicians of the first and second centuries A.D. treating constipation with senna pods and using caraway and peppermint to relieve digestive upset.

Throughout the middle ages, home-grown botanicals were the only medicines readily available and for centuries, no self-respecting household would be without a carefully tended and extensively used herb garden. For the most part, herbal healing lore was passed from generation to generation by word of mouth, such as a mother taught a daughter, father taught a son, the village herbalist to a promising apprentice etc.

By the 17th century, the knowledge of herbal medicine was widely disseminated throughout Europe. In 1649, Nicholas Culpeper wrote "A Physical Directory" and a few years later produced "The English Physician". This respected herbal pharmacopeia was one of the primary manuals, that the layperson could use for health care and it is still widely referred even today. Culpeper had studied at Cambridge.
University and wanted to become a great doctor, in the academic sense of the word. Instead, he chooses to apprentice to an apothecary and eventually set up his own shop. He served the poor people of London and became known as their neighborhood doctor. The herbal formulation he created was meant for the layperson.

The first U.S. Pharmacopeia was published in 1820. This volume included an authoritative listing of herbal drugs with descriptions of their properties, uses, dosages and tests of purity. It was periodically revised and became the legal standard for medical compounds in 1906. But, as Western medicine evolved from an art to a science in the 19th century, information that had at one time been widely available became the domain of comparatively few. Once scientific methods were developed to extract and synthesize the active ingredients in plants, pharmaceutical laboratories took over from providers of medicinal herbs as the producers of drugs. The use of herbs, which for most of history had been mainstream medical practice, began to be considered unscientific, or at least unconventional, and to fall into relative obscurity.

In India, the herbalist tradition was Ayurvedic, focusing on the use of metals, herbs and parts of animals generally considered inedible, prepared in solution. These herbs and other compounds are used in varying proportions to cure specific diseases and may be applied internally as pills or infusions, topically as ointments, inhaled as smoke, or pressed to the body as powders.

In the Americas, without a written tradition to work from, most herbalism is carried by oral traditions from various tribes; this has proven invaluable when looking for herbal remedies in the rain forests and uplands. Much of the American herbal tradition tied to follow shamanism and spiritualism.

In the early 19th century, when chemical analysis first became available, scientists began to extract and modify the active ingredients from plants. Later, chemists began making their own version of plant compounds and over the time, the use of herbal medicines declined.
1.1.2 *HISTORICAL OVERVIEW OF INDIAN SYSTEM OF MEDICINE*

India has an ancient heritage of traditional medicine. *Materia Medica* of India provides lots of information on the folklore practices and traditional aspects of therapeutically important natural products. Indian traditional medicine is based on Botanicals. The Indian Traditional Medicine based on various systems including *Ayurveda*, *Siddha*, *Unani* and others. The evaluation of these drugs is mostly based on Pharmacognostical, Phytochemical, Pharmacological and allied approaches including various instrumental techniques like chromatography, microscopy and others. These traditional systems of Indian medicine have their uniqueness, but there is a common thread running through these systems in their fundamental principles and practices. With the emerging interest in the world to adopt and study the traditional system and to exploit their potentials based on different healthcare systems, the Government of India is trying their best to explore all possibilities for the evaluation of these systems to bring out therapeutic approaches available in original system of medicine as well as to help in generating data to put these products on national health care programme.\(^1\)

1.1.3 *INDIAN SYSTEMS OF MEDICINE*

Besides *Ayurveda* there are several other complementary and alternative systems of medicine like *Homeopathy*, *Siddha* and *Unani* systems of medicine, which are also practiced and developed in course of time in India, where plants and plant based formulations are employed for health care and disease treatment. Some of the well-known ancient *Ayurvedic* texts are the *Charka Samhita* (CS), *Sushruta Samhita* (SS), *Ashtanga Hridaya* (AH) (600 AD), and *Madhav Nidan* (MN). The chronologic origins of *Ayurveda* (varies from 1000–6000 B.C in the literature), especially with reference to the CS and SS are still controversial.\(^1\)

1.1.3.1 *The Siddha system of medicine*

This system is developed since the ancient human civilization in India. Like *Ayurveda*, it is developed through day-to-day experiences of using natural resources for health care. The *Siddha* system is one of the oldest systems of medicine in India.
According to traditional belief Lord Shiba unfolded the knowledge of medicine to his wife Parvati, which was then passed to Siddhars. The term 'Siddha' means achievement and the 'Siddhars' were saintly figures who achieved results in medicine through the practices. The system is believed to be developed by 'Siddhars' who glorified human being as the highest form of birth and believed that preserving the human body is essential to achieve the eternal bliss. The principles and concepts of this system are closely similar to those of Ayurveda, with specialization in Iatrochemistry. As in Ayurveda, this system also considers the human body as a conglomeration of three humors, seven basic tissues and the waste products. The equilibrium of humors is considered as health and its disturbance or imbalance leads to disease or sickness. The system describes 96 principal constituents of a human being which include physical, physiological, moral and intellectual components. When there is any change or disturbance in functioning of these principals, body as a system deviates towards the cause of disease. The diagnostic methodology in the Siddha system is eight-fold, including examination of pulse, tongue, complexion, speech; palpatory findings so on and so forth. Perception has a great role in this venture; this can be achieved by sensory organs, by mind, by yoga, by pain and pleasure. The Siddha system is a psychosomatic system, where attention is given to minerals and metals along with plant constituents. [6]

1.1.3.2 Unani Medicine

It is based on the Greek philosophy. The drugs used are mostly of the plant origin. Some drugs of animal and mineral origin are also used. Patients are treated either by single drug (crude drug) or by compound drugs (formulation of crude drugs). There are two types of compound drugs used in the treatment of the diseases i.e., Classical compound drugs which are in use for the hundreds and thousands of years and Patent/Proprietary compound drugs which have been formulated by the individuals or Institutions as per their research and experiences. [1] In this particular traditional system, single drug or their combinations in raw form are preferred over compound formulation. The system offers time-tested remedies for gastrointestinal, cardiovascular and nervous disorders. The naturally occurring drugs used in this system are symbolic of life and generally free from side effects. At present the Unani
system of medicine, with its own recognized practitioners, hospitals and educational research Institutions forms an integral part of the national health care system.  

1.1.3.3 Homeopathy Medicine

Homeopathy's roots emerge from the findings, teachings and writings of Dr. Samuel Hahnemann (1755-1843). Hahnemann graduated from medical school in 1779 and started his own medical practice. He soon began his first homeopathic experiments in 1790, as a result of his disillusionment with such common medical practices of the day as purging, blood letting, and the use of toxic chemicals. At one point, he gave up his own daily practice to begin working as a chemist while translating medical texts. It was when Hahnemann began working on a project to translate William Cullen's *Materia Medica* into German that he began his quest for a better way of providing healthcare using the principles of "Similars." While working on this project, he became fascinated with a species of South American tree-bark (cinchona) which was being used to treat malaria-induced fever. Hahnemann ingested the bark and discovered that it caused symptoms similar to malaria. He continued his research into "cures" and the idea of "similar suffering," and began compiling his findings. Similia similibus curentur, the Latin phrase meaning "let likes be cured by likes," is the primary principle of homeopathy.

1.1.3.4 Plants used in different systems of medicines in India

Plants and plant-derived products are part of health care system since ancient human civilizations. The need of new chemical entities (NCEs) for health care is explored and served through the plant sources. In India, the history of health care goes back to 5000 years B.C., when health care needs and diseases were noted in ancient literatures like 'Rig-Veda' and 'Atharva-Veda'. Later, the texts like 'Charaka Samhita' and 'Sushruta Samhita' were documented in about 1000 years B.C., where use of plants and poly-herbal formulations were highlighted for health care. Evolution of *Ayurveda* and plant-based remedies for health care through day-to-day life experiences is a part of cultural heritage of India.

The WHO document includes many topics such as development of protocols for clinical trials using herbal medicines, evaluation of herbal medicine research,
guidelines for quality specifications of plant materials and preparations, and guidelines for pharmacodynamic and general pharmacological studies of herbal medicines and investigations of toxicity of herbal medicines.

WHO has also issued guidelines for the assessment of Herbal medicines (WHO, 1996). These guidelines defined the basic criteria for the evaluation of quality, safety and efficacy of herbal medicines with the goal of assisting national regulatory authorities, scientific organizations and manufacturers in assessing documentation, submissions and dossiers in respect of such products. It was recommended that such assessments take into account for long-term use in the country (over at least several decades), any description in the medical and pharmaceutical literature or similar sources or documentation of knowledge on the application of a herbal medicine, and marketing authorizations for similar products. Although prolonged and apparently uneventful use of a substance usually offers testimony of its safety, investigation of the potential toxicity of naturally occurring substances may reveal previously unsuspected problems. It was also recommended that regulatory authorities have the authority to respond promptly to new information on toxicity by withdrawing or limiting the licences of registered products containing suspect substances, or by reclassifying the substances to limit their use to medical prescription. The guidelines stressed the need for assessment of efficacy including the determination of pharmacological and clinical effects of the active ingredients, and labelling which includes a quantitative list of active ingredient(s), dosage and contraindications.

Undoubtedly plants have provided useful drugs to mankind for his health care and other needs. The efforts to combat the diseases, for which there are no satisfactory solutions as yet, should be continued relentlessly. Hopefully plant kingdom will help us in discovering new drugs useful for the alleviation of human illness.

According to a survey by WHO plants used in different system of traditional medicine is given below.\textsuperscript{11, 21}
1.2 DIABETES MELLITUS

Diabetes Mellitus (DM) is a group of syndrome characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins and an increased risk of complications from vascular disease. Most patients can be classified clinically as having either type-I DM is also known as insulin dependent diabetes mellitus (IDDM) type-II DM is also known as non-insulin dependent diabetes mellitus (NIDDM)

The incidence of each type of diabetes varies widely throughout the world. The vast majority of diabetes patients have type-II DM. In the United States, about 90% of all diabetes patients have type-II DM. There are 130 million persons having diabetes in the world today. Type I and type-II DM both are increasing in frequency. The reason for increase in type-I DM is not known. The general basis for type-II DM cannot change in such a short time. Thus, other contributing factors including increasing age, obesity, sedentary lifestyle and low birth weight must account for this dramatic increase. In addition, type-II DM is now being diagnosed with remarkable frequency in preadolescents and adolescents.
There are genetic and environmental components to both type-I DM and type-II DM. Virtually all forms of diabetes mellitus are caused by a decrease in the circulating concentration of insulin (insulin deficiency) and a decrease in the response of peripheral tissue to insulin (insulin resistance). These abnormalities lead to alterations in the metabolism of carbohydrates, lipids, ketones and amino acids.

Insulin lowers the concentration of glucose in blood by inhibiting hepatic glucose production and by stimulating the uptake and metabolism of glucose by muscle and adipose tissue. These two important effects occur in different concentrations of insulin. Production of glucose is inhibited by half maximally by an insulin concentration of about 20 μU/ml, and glucose utilization is stimulated by half maximally at about 50 μU/ml.

In both type of DM, glucagons oppose the effect of insulin in the liver by stimulating glycogenolysis and gluconeogenesis. But, it has relatively little effect on peripheral utilization of glucose. Thus, in the diabetic patient with insulin deficiency or insulin resistance and hyper glucagonemia, there is an increase in hepatic glucose production, a decrease in peripheral glucose uptake and a decrease in the conversion of glucose to glycogen in the liver. [7]

1.2.1 Diabetes status in India

Diabetes has an ancient origin. Susruta, father of Indian medicine diagnosed DM as early as 1000 B.C. Ayurveda mentioned that insects and flies were attracted to the urine of some people and that the urine tasted sweet. Greek physicians further refined the diagnosis of dypsacus (diabetes) associated with weakness of kidneys and excess release of moisture from the body, leading to dehydration. The Greeks advised that all diuretic food and drugs be avoided and that patients with diabetes mellitus should be engaged in exercise.

The discovery of insulin by Banting and Best (1922) is the key milestone in the treatment of diabetes mellitus. Insulin is a life saving drug in treatment of diabetes mellitus. However, insulin is required to be administered by parenteral route. A search of drugs which can be administered orally was made. After the synthesis and
evaluation of some earlier compounds tolbutamide was the first compound available for the treatment of diseases. [8]

1.2.2 The Changing Scenario

Diabetes seems to be receiving a lot of attention recently in India. Earlier classified as the “rich man’s disease”, it has now spread amongst the masses. India is slated to be the diabetic capital of the world by 2025. There were 24 million diabetics in the year 2000 and this figure is expected to reach 57.02 million by 2025.

Several factors are said to be contributing to the prevalence of diabetes in India. The most common are factors like stress, sedentary lifestyle and consumption of food having little nutritional value. The rural to urban ratio is on the decline; in 2000 this was about 30:70. The literacy rate has risen by about 10% in the last decade. The middle class has burgeoned to 22.2% of the total population. Apart from these, several other theories have come up to explain the growing incidence of diabetes. The “thrifty genotype” theory states that, there are strong genetic component in the etiology of type-II diabetes mellitus that typically affects people over 40 years of age. The theory proposes, when individual with a thrifty genotype are exposed to a continuous supply of energy dense food coupled with reduction in physical activity, obesity and impaired glucose tolerance leading to type-II diabetes. This along with rapid change from a normal traditional and rural life style to a westernized one leads to rise in type-II diabetic population. Further, Indians tend to become diabetic at a relatively young age of 45 years which is about 10 years earlier than that in western countries. The development of new and effective drugs in DM has become a major research area of national and international importance. [8]

1.3 Hypertension

High blood pressure (HBP) or hypertension (HTN) means high pressure (tension) in the arteries. Arteries are vessels that carry blood from the pumping heart to all the tissues and organs of the body. High blood pressure does not mean excessive emotional tension, although emotional tension and stress can temporarily increase blood pressure. Normal blood pressure is 120/80; blood pressure between 120/80 and
139/89 is called "pre-hypertension", and a blood pressure of 140/90 or above is considered as hypetension.

The top number, the systolic blood pressure, corresponds to the pressure in the arteries as the heart contracts and pumps blood forward into the arteries. The bottom number, the diastolic pressure, represents the pressure in the arteries as the heart relaxes after the contraction. The diastolic pressure reflects the lowest pressure to which the arteries are exposed.

An elevation of the systolic and/or diastolic blood pressure increases the risk of developing heart (cardiac) disease, kidney (renal) disease, hardening of the arteries (atherosclerosis or arteriosclerosis), eye damage, and stroke (brain damage). These complications of HTN are often referred to as end-organ damage because damage to these organs is the end result of chronic (long duration) high blood pressure. For that reason, the diagnosis of HBP is important. So that efforts can be made to normalize blood pressure and prevent complications.

It was previously thought that rise in diastolic blood pressure was a more important risk factor than systolic elevations. But, it is now known that in people 50 years or older, systolic hypertension represents a greater risk factor.

The American Heart Association estimates that HBP affects approximately one in three adults and around 73 million people in the United States. HBP is also estimated to affect about two million American teens and children, and the Journal of the American Medical Association reports that many are under-diagnosed. HTN is clearly a major public health problem.

HBP is often called the silent killer because in the initial stages it presents with no symptoms. It is only after an organ in the body is irritated or damaged, the consequences of high blood pressure are realized.

The blood pressure recording, measures pressures within the arteries at two different times. The first reading, the systolic pressure, measures the pressure when the heart is pumping blood to the body through the arteries. The second reading, the diastolic pressure, measures the pressure within the arteries when the heart is receiving blood.
returning from the body. Blood pressure measurement is listed with two numbers with normal being 120/80, with 120 being the systolic blood pressure when the heart is pushing blood through the arterial system; and 80 being the diastolic blood pressure when the arteries are at rest and the heart is refilling. [9]

1.3.1 **Hypertension in Diabetes Mellitus Patients**

Management of hypertension in diabetics demands special attention, more so in Indian scenario. Higher prevalence of HTN amongst diabetics in India has been reported since 1985. [10] Review on the subject by Das (1995, on Indian data) had revealed the prevalence to be as variable as 7% in Cuttack to 30.9% in Sevagram. Further, there was a variable difference between IDDM (Type-I) and NIDDM (Type-II) i.e., 10% and 32% respectively in diabetics from Mumbai. [11] Recent studies from Manipal revealed about 40% diabetics to be hypertensive. [12] Such higher prevalence of HTN could partly be due to better assessment in diabetics but most likely on par with change of lifestyle and increase in the prevalence of non-communicable diseases in rapidly growing economies. Consequently, cardiovascular diseases (CVD) in diabetics will account for 5 to 20% of the total health care expenditure. A number of modifiable arterial risk factors contribute to the higher prevalence of CVD in patients with diabetes mellitus (DM). [13] Hypertension is one of the modifiable arterial risk factors for developing CVD.

1.3.2 **Types of Hypertension in Diabetes Mellitus**

1. Essential hypertension
2. Hypertension consequent to nephropathy
3. Isolated systolic hypertension
4. Supine hypertension with orthostatic fall

Possible mechanisms in pathogenesis
A. Uncontrolled metabolic state
B. Insulin resistance leading to abnormalities in:
i) Renal tubular ion exchange.

ii) Transmembrane ion exchange in vascular bed.

iii) Renin angiotensin system.

iv) Prostaglandinkallikrein/kinin system.

v) Inter-relationship with Mg.

vi) Aterial natriuretic peptide.

vii) Diabetic nephropathy.

viii) Sympathetic nervous system involvement.

ix) Other endocrine syndromes/secondary causes.

1.3.3 GUIDELINES FOR THE MANAGEMENT OF HYPERTENSION

Despite the fact that patients who suffer from both DM and HTN could represent a complex entity as regards developing CVD, short comments have been made in the JNC VI report on the treatment of HTN in diabetic subjects. In view of the importance of the problem the issue needs to be discussed under three specific areas, viz.:

1. Which measurement of arterial blood pressure should be considered?

2. Which arterial pressure target value should be considered?

3. Which treatment modalities should be proposed as an optimal strategy?

Measurement of arterial blood pressure (ABP) is defined as systolic blood pressure (SBP) of 140 mmHg or greater and/or diastolic blood pressure (DBP) of 90 mm Hg or greater. The object of identifying and treating high blood pressure is to reduce the risk of CVD and associated morbidity and mortality. Therefore, It is imperative to provide a classification of blood pressure in adults so as to identify the high risk individuals and to provide guidelines for treatment and follow-up.
Table 1-1. Classification of blood pressure for adults (JNC VI report)

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt; 120</td>
<td>and &lt; 80</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 130</td>
<td>and &lt; 85</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139</td>
<td>or 85-89</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160-179</td>
<td>or 100-109</td>
</tr>
<tr>
<td>Stage 3</td>
<td>equal/above 180</td>
<td>or above 110</td>
</tr>
</tbody>
</table>

Supine, sitting, and standing blood pressure should be measured in all diabetic subjects. This is an important issue in diabetic patients where autonomic neuropathy often leads to supine HTN with postural fall of blood pressure. Arterial blood pressure measured in the sitting position should be considered as ideal.

The incidence and prevalence of type-II diabetes are increasing. It is projected that the total number of people with diabetes will rise from 171 million in 2000 to 366 million by 2030. It is predicted that the number of adults with hypertension is to increase by 60% to a total of 1.56 billion people by 2025. HTN affects approximately 70% of patients with diabetes. The prevalence of coexistent hypertension and diabetes varies across different ethnic, racial and social groups. Importantly, HTN in patients with diabetes causes a significant increase in the risk of vascular complications in this population and together both conditions predispose to chronic kidney disease. The overlap between hypertension and diabetes substantially increases the risk of ischemic cerebro-vascular disease, retinopathy and sexual dysfunction. Diabetes mellitus is an independent risk factor for coronary artery disease and the risk is markedly increased when hypertension is present.
Diabetic nephropathy is the commonest cause of HTN in patients with type-I diabetes. Patients with type-II diabetes can develop renal disease, but hypertension commonly occurs without abnormal renal function and is often associated with central obesity. Insulin resistance and diabetes can precipitate HTN by stimulating the sympathetic nervous system and the rennin-angiotensin system and by promoting sodium retention. Diabetes is also associated with increased proliferation of vascular smooth muscle cells. High blood glucose and elevated blood pressure can impair vascular endothelial cells leading to increased oxidative stress. Patients with diabetes also have increased vascular reactivity.\textsuperscript{[14]}

In addition to a major impact on clinical care, quality of life and public health, DM and HTN account for significant health care expenditure. The compelling evidence linking these diseases, mostly its association and interaction with morbid conditions prompt clinical awareness.\textsuperscript{[15]}

There are some herbs like Ginseng, Ginkgo biloba and Bilberry leaves, which are proved pharmacologically for their both anti-diabetic and antihypertensive activities.

We have selected a very common weed \textit{Scoparia dulcis} Linn. for the present project work. It is used by \textit{Vaidyas} of western Odisha for the treatment of both diabetes and hypertension. Its root is traditionally used as an effective remedy for Jaundice and diarrhoea. It is also used as diuretic to treat HTN. This plant is widely available in each and every part of Odisha and India. Its literature and traditional uses exemplify the plant has both anti-diabetic and antihypertensive activities.

During literature survey it was observed that the plant \textit{Scoparia dulcis} Linn. is widely used by the tribals for various ailments. However, the plant as a whole has not yet been systematically and scientifically characterized and documented.

Our aim is to screen the plant phyto-pharmacologically, so that the plant \textit{Scoparia dulcis} may be utilized by the pharmaceutical companies as a potent anti-diabetic and antihypertensive drug, both at national and global level.
1.4 REVIEW OF *SCOPARIA DULCIS* LINN.

1.4.1 PLANT PROFILE

1.4.1.1 Vernacular Name

<table>
<thead>
<tr>
<th>Language</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odia</td>
<td>Mithi Patti</td>
</tr>
<tr>
<td>Hindi</td>
<td>GhodaTulsi, Ban Dhania</td>
</tr>
<tr>
<td>English</td>
<td>Sweet broom, Broomweed, Vassourinha</td>
</tr>
<tr>
<td>Sanskrit</td>
<td>Pashanabheda, Asmghni</td>
</tr>
</tbody>
</table>

Synonyms: *Scoparia grandiflora, Scoparia ternata,*

*Capraria dulcis, Gratiolamicrantha*

1.4.1.2 Taxonomy

<table>
<thead>
<tr>
<th>Taxonomic Level</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Subkingdom</td>
<td>Trachcobionta</td>
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<tr>
<td>Division</td>
<td>Magnoliophyta</td>
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<tr>
<td>Class</td>
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<tr>
<td>Family</td>
<td>Scrophulariaceae</td>
</tr>
<tr>
<td>Genus</td>
<td><em>Scoparia</em></td>
</tr>
<tr>
<td>Species</td>
<td><em>dulcis</em></td>
</tr>
</tbody>
</table>

Botanical name: *Scoparia dulcis* Linn.
1.4.1.3 Description

*Scoparia dulcis* Linn. is an annual erect herb; profusely branched, the younger stems are 5-to 6-angled, glabrous. Leaves are 3-nately whorled, simple; extipulate; petioles short or subsessile; laminae broadly elliptic to oblanceolate, bases attenuate, margins serrate, tips acute, unicostate, reticulate and the surfaces are glabrous. Inflorescences axillary cymes, 1 to 2 flowered. Flowers are ebracteate, ebracteolate, pedicellate, bisexual, actinomorphic, tetramerous, hypogynous. Calyx aposepalous, the sepals 4, imbricate in bud, persistent. Corolla synpetalous, 4-fid, rotate, tubes short, throat densely bearded, the lobes obtuse, subequal, white. Androecium polyandrous, stamens 4, didynamous, epipetalous, filaments filiform, attached at the base of corolla tube, exserted, anthers dithecous, subsagittate, dorsifixed, introrse, dehiscence longitudinal. Pistil present is 1, ovary; ovoid or globose, 2-carpeled, syncarpous, 2-loculed, placentation axile, ovules numerous on the enlarged placentae, style subclavate, stigmas bifid. Fruit is septicidal capsule, globose, valves membranous, the margins inflexed; seeds many, obovoid, endosperm fleshy. **Flowering period**: October - December. **Fruiting period**: November – January.¹⁵¹
1.4.1.4 Distribution:

*Scoparia dulcis* is a medicinal herb distributed throughout tropical and subtropical regions of India, America, Brazil, West Indies, and Myanmar. It is introduced in India from tropical America. [2, 5] *S. dulcis* (Mala-anis) is a ubiquitous weed, a native of tropical America, found in the Philippines, in and about towns throughout the settled areas at low and medium altitudes. According to Dalziel when chewed, the plant is at first bitter and later sweet.

Sweet-broom, a widespread herb in the tropics, is commonly found as a weed near houses. It would go too far to say it was cultivated, but it is at least tolerated. The most common references to it are its use as broom/stems. These are bundled and used to clean the area around and within homes. This practice is very old and has been reflected in the scientific as well as most of the common names. The name *Scoparia dulcis* was applied by Linnaeus in 1753. [6,16-18]
1.4.2 ETHNO-PHARMACOLOGY

1.4.2.1 Traditional Uses

The whole plant boiled in water is taken internally for diseases like diarrhoea, stomach-ache, kidney stones, kidney problems, fever etc. It is used as a gargle in the cure for tooth-ache. The root is considered as astringent, mucilaginous and emollient, it is also used as a medicine for blennorrhagia and in excessive menstruation.

Aerial Parts: Coughs, diarrhoea, expectorant, fever and stomach pains. [23-27]

Whole Plant: Anemia, bronchitis, burns, coughs, diabetes, diarrhoea, dysentery, expectorant, fever, gastric disorders, headache, hemorrhoids, hepatitis, hypertension, infections, insect bites, intestinal worms, jaundice, liver disease, gout, malaria, gonorrhoea, childbedbirth, menstrual disorders, pain, rash, snake bites, swelling and toothache. [23-29]

Leaf: Diabetes, diarrhoea, eye problems, fever, headaches, hemorrhoids, infections, insect bites, intestinal worms, kidney disease, liver disorders, malaria, menstrual disorders, migraines, snake bites, stomach disorders, tonic, ulcers, urinary tract disorders, sex weakness, vomiting, wounds, anemia, burns and cough. [24-25]

Root: Bronchitis, diarrhoea, fever, jaundice, liver disorders, malaria, menstrual disorders, skin infections and stomach pains. [28-29]

Internal: Vassourinha is primarily used in herbal medicine for upper respiratory problems, viruses, for menstrual problems, as a natural analgesic and antispasmodic remedy when needed. The Chak and Murong tribes inhabit the Chittagong Hill Tracts forest region of Bangladesh. They rely mostly on their traditional medicinal practitioners for cure of various ailments. They collected information on medicinal plants used to treat gastrointestinal disorders by conducting questionnaires. They found that Scoparia dulcis can be used for the treatment of gastrointestinal disorders. The plants or plant parts are used as remedy for stomachpain, intestinal worms, diarrhoea, dysentery, blood dysentery, flatulence, acidity, constipation and hardening of stools. In the Philippines, the roots, leaves and tops are used in the form of infusion against gastralgias, diarrhoea and dysentery. A decoction of the root is said to be good...
for fevers also. Guerrero reports that an infusion of the leaves and tops is used as a tea in certain infection of the intestines. Leaf extract is taken orally to cure kidney stone.\\[26\\] Fruit juices, seed extract and leaf extract is helpful in urinary stone prophylaxis.\\[27\\]

**External:** Externally the plant has been used traditionally to treat skin wounds and infections, insect bites, snakebites, burns, rashes, eye problems, ulcers, fevers and headaches.\\[19-27\\]

### 1.4.3 Phytoconstituents

*S. dulcis* or Vassourinha is rich in flavones, terpenes and steroids. The main chemicals include scopadulcic acids A and B, scopadiol, scopadulciol, scopadulin, scoparic acids A-C and betulinic acid. Other chemicals include: acacetin, amyrin, apigenin, benzoazoxin, benzoazolin, benzoazolinone, cirsimarin, cirsitakaoside, coixol, coumaric acid, cynaroside, daucosterol, dulcinol, dulcioic acid, friedelin, gentisic acid, glutinol, hymenoxin, ifflaionic acid, linarin, luteolin, mannitol, scoparinol, scutellarein, scutellarin, sitosterol, stigasterol, tannin, taraxerol, vicenin, vitexin.

### 1.4.3.1 Phytochemical Screening

Alkaloids are present in entire plant, flavonoids are present in flowers, and saponins are present in shoots and root.\\[28,29\\]

The available literature on phytochemical reports of the *S. dulcis* reveals that it comprises mainly terpenes and flavones. Figure 1.4 to 1.39 summarizes phytoconstituents reported from various plant parts of *S. dulcis*. We have arranged all the phytochemicals reported along with their biological activities individually.
Structure of the phytoconstituents

![Figure 1.4. Str. of Scopadulcic Acid A](image1)

**Compound: Scopadulcic Acid A**
**(Diterpene)**

Molecular Formula (M.F.) - C\(_{27}\)H\(_{34}\)O\(_6\)

Melting point (m.p.) - 172-174°C

Biological activity: Falciparum malaria.

![Figure 1.5. Str. of Scopadulcic Acid B](image2)

**Compound: Scopadulcic Acid B**
**(Diterpene)**

Molar Formula (M.F.) - C\(_{27}\)H\(_{34}\)O\(_5\)

M.p. - 228-232°C

Biological activity: Antiviral, antitumor activity in various human cell lines.

![Figure 1.6. Str. of Scoparic Acid A](image3)

**Compound: Scoparic Acid A**
**(Diterpene)**

Molar Formula (M.F.) - C\(_{27}\)H\(_{36}\)O\(_5\)

M.p. - Colorless amorphous powder

\([\alpha]D\)\(_{26}^{26}\) = 38.3° (c = 1.00, CHCl\(_3\))

Biological activity: \(\beta\)-glucuronidase inhibition.

![Figure 1.7. Str. of Scoparic Acid B](image4)

**Compound: Scoparic Acid B**
**(Diterpene)**

Molar Formula (M.F.) - C\(_{25}\)H\(_{32}\)O\(_5\)

M.p. - Colorless amorphous powder

\([\alpha]D\)\(_{23}^{23}\) = -9.8° (c = 0.63, CHCl\(_3\))

Biological activity: Antiviral.
Compound: Scoparic Acid C  
(Diterpene)  
M.F.- $C_{26}H_{32}O_5$  
m.p.- colorless amorphous powder  
Biological activity: $\beta$-glucuronidase inhibition.

Compound: Apigenin (Flavone)  
M.F.- $C_{15}H_{10}O_5$  
m.p.- 315°C  
yellow crystalline powder  
Biological activity: Antioxidant, radical scavenger, anti-inflammatory, carbohydrate metabolism promoter, immunity system modulator.

Compound: Acacetin (Flavone)  
M.F.- $C_{16}H_{12}O_5$  
m.p.- 268-272°C  
Pale-yellow needles  
Biological activity: Inhibits Human Atrial Repolarization Potassium Currents, antioxidant, radical scavenger, anti-inflammatory, carbohydrate metabolism promoter, immunomodulator.

Compound: Amyrin, alpha (Triterpene)  
M.F.- $C_{30}H_{50}O$  
m.p.- 188°C  
White crystalline powder  
Biological activity: Anti-elastase activity, and modulates the membrane fluidity PGE2 release inhibition, strong anti-inflammatory activity, PKA inhibitor as well as a selective protease inhibitor.
**Compound**: Benzoxazin-3-one, 1-4: 2(h): 2-hydroxy (Nitrogen heterocy)

M.F.: C₆H₇NO₂  

m.p.: 172-176 °C  

Biological activity: Antimicrobial, anticancer and anti-inflammatory.

**Compound**: Benzoxazolinone (Nitrogen heterocy)

M.F.: C₆H₅NO₂  

m.p.: 82-86°C  

Light brown-pink Crystalline powder  

Biological activity: Adrenergic and antihypertensive properties.

**Compound**: Betulinic Acid (Triterpene)

M.F.: C₃₀H₄₈O₃  

m.p.: 295-298 °C (decomposes)  

White crystalline powder  

Optical Rotation: +7° - +9° (c=0.9 in pyridine)  

Biological activity: Potential anti-melanoma agent, effective as a NSAID, anti-malarial, anti-HIV, prostaglandin antagonist.

**Compound**: Benzoxazolin-2-one, 6-methoxy (Nitrogen heterocy)

M.F.: C₆H₇NO₃  

m.p.: 151-156 °C (lit.)  

Light tancolour  

Biological activity: Antimicrobial and anti-inflammatory.
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Figure 1.16. Str. of Cirsimarin

Compound:Cirsimarin (Flavone)
M.F.-C_{23}H_{24}O_{11}
m.p.- 244-246 °C
Biological activity: Stimulate lipolysis, anti-inflammatory, anti-diabetic and hypotensive.

Figure 1.17. Str. of Benzoxazolone, 2(3H) 6-methoxy

Compound:Benzoxazolone, 2(3H) 6-methoxy (Nitrogen heterocycle):
M.F.-C_{8}H_{7}N_{0}3
m.p.- 152-156 °C
Biological activity: Antimicrobial, analgesic and anti-inflammatory.

Figure 1.18. Str. of Cirsitakaoside

Compound:Cirsitakaoside (Flavone)
M.F.-C_{23}H_{24}O_{11}
m.p.- 246-247 °C
Biological activity: Respiratory disease, gastric, hepatic disturbances, anti-inflammatory, anti-diabetic and hypotension.

Figure 1.19. Str. of Cynaroside

Compound:Cynaroside (Flavone)
M.F.-C_{21}H_{20}O_{11}
m.p.- 266-268 °C
Yellow amorphous powder
Biological activity: Antioxidant, anti-diabetic.
INTRODUCTION

**Figure 1.20. Str. of Coumaric Acid**

[49]

**Compound:** Coumaric acid, para (Phenylpropanoid)

M.F.: C₇H₆O₃

m.p.: 210–213 ºC

Biological activity: Inhibits the development of stomach cancer.

**Figure 1.21. Str. of Dulcitol**

[50]

**Compound:** Dulcitol (Diterpene)

M.F.: C₈H₁₄O₆

m.p.: 188–189 ºC

Biological activity: Antiviral and cytotoxic activity.

**Figure 1.22. Str. of Daucosterol**

[51]

**Compound:** Daucosterol (Steroid)

M.F.: C₃₅H₆₀O₆

m.p.: 295 ºC

Biological activity: Immunomodulator

**Figure 1.23. Str. of Dulcioic Acid**

[44]

**Compound:** Dulcioic Acid (Triterpene)

M.F.: C₃₀H₄₈O₃

m.p.: 300 ºC

Biological activity: Significant inhibitory effect on cytokine production, anti-spasmodic.
### Compound: Friedelin (Triterpene)
- M.F.: C_{30}H_{50}O
- m.p.: 262-265 °C
- Biological activity: Estrogenic, anti-inflammatory, analgesic and antipyretic.

### Compound: Gentisic acid (Benzenoid)
- M.F.: C_7H_6O_4
- m.p.: 200 - 205 °C
- Biological activity: Antispasmodic, local anesthetic, antioxidant and anticonvulsant.

### Compound: Glutinol (Triterpene)
- M.F.: C_{30}H_{50}O
- m.p.: 206-208°C
- Biological activity: Anti-inflammatory, analgesic.

### Compound: Hymenoxin (Flavone)
- M.F.: C_{19}H_{18}O_8
- m.p.: -215- -216°C
- Biological activity: Estrogenic, anti-spasmodic.
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Figure 1.28. Str. of Ifflaionic Acid
[58, 59]

**Compound:** Ifflaionic Acid
*(Triterpene)*
M.F.: C$_{30}$H$_{46}$O$_{3}$
m.p.: 330°C

Biological activity: Hypotensive

Figure 1.29. Str. of Linarin
[60]

**Compound:** Linarin (Flavone)
M.F.: C$_{28}$H$_{32}$O$_{14}$
m.p.: 258-260°C

Biological activity: Sedative and sleep-enhancing properties.

Figure 1.30. Str. of Luteolin
[61-64]

**Compound:** Luteolin (Flavone)
M.F.: C$_{15}$H$_{10}$O$_{6}$
m.p.: 330°C

Yellow crystalline compound

Biological activity: Anti-oxidant, anti-cancer, immunomodulator, anti-inflammatory.

Figure 1.31. Str. of Mannitol, d
[65, 66]

**Compound:** Mannitol, d(Carbohydrate)
M.F.: C$_{6}$H$_{14}$O$_{6}$
m.p.: 164 - 169°C

White crystalline compound

Biological activity: Diuretic, Alzheimer's disease, chemotherapy for brain tumors.
**INTRODUCTION**

**Figure 1.32. Str. of Scutellarein**

Compound: Scutellarein (Flavone)
M.F.- C\(_{21}\)H\(_{18}\)O\(_{12}\)
m.p.- 218-220 °C
Biological activity: Induce apoptosis of ovarian and breast tumor cells in vitro.

**Figure 1.33. Str. of Scoparinol**

Compound: Scoparinol (Diterpene)
M.F.- C\(_{27}\)H\(_{38}\)O\(_{4}\)
m.p.-
Biological activity: Anti-inflammatory, analgesic.

**Figure 1.34. Str. of Sitosterol, beta**

Compound: Sitosterol, beta (Steroid)
M.F.- C\(_{29}\)H\(_{5}\)O
m.p.- 136-140 °C
Biological activity: Antioxidant, anti-cancer, anti-tumor, reduce blood cholesterol levels.

**Figure 1.35. Str. of Stigasterol**

Compound: Stigasterol (Steroid)
M.F.- C\(_{29}\)H\(_{48}\)O
m.p.- 161-170 °C
Biological activity: Anti-cancer, lower serum cholesterol, antioxidant, hypoglycemic.
Chapter-1

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**Figure 1.36. Str. of Taraxerol**

[72]

**Compound: Taraxerol (Steroid)**
M.F.: C_{30}H_{50}O
m.p.: 282-285°C
Biological activity: Anti-cancer, anti-tumor.

**Figure 1.37. Str. of Vicenin 2**

[73-75]

**Compound: Vicenin 2 (Flavone)**
M.F.: C_{27}H_{30}O_{15}
m.p.: 271-272°C
Biological activity: Anti-cancer, anti-inflammatory.

**Figure 1.38. Str. of Vitexin**

[76, 77]

**Compound: Vitexin (Flavone)**
M.F.: C_{21}H_{20}O_{10}
m.p.: 256-257°C
Biological activity: Antioxidant, hypotensive.

**Figure 1.39. Str. of Vitexiniso**

[76, 77]

**Compound: Vitexin, iso (Flavone)**
M.F.: C_{21}H_{20}O_{10}
m.p.: 203-204°C
Biological activity: Antioxidant, hypotensive.
1.4.4 REVIEWS OF PHYTOCHEMICAL SCREENING

The phytochemical screening of the *Scoparia dulcis* Linn. \[30\] revealed that, it is rich in flavonoids and terpenes. The pharmacological action of the herb is believed to be due to the presence of these phytochemicals.

The analgesic and anti-inflammatory activities of water and ethanolic extract of *S. dulcis* were investigated in rats and mice. These effects were compared with the effect induced by Glutinol isolated by purification of ethanolic extract of *S. dulcis*. The results indicate that the analgesic activity of *S. dulcis* L. may be explained by an anti-inflammatory activity probably related to the triterpene Glutinol.\[78\]

*Hayashi et al. (1997)\[79\] reported that production of scopadulcic acid B and scopadulciol by leaf organ culture of *S. dulcis* has been examined by addition of cytokinins to culture media.*

*Health Sciences Institute (2001)\[80\]*

Much of the recent research on *S. dulcis* has centered around one powerful phytochemical called scopadulcic acid B (SDB). In a clinical study in 1993, SDB inhibited the growth of tumors in a test tube and in mice. Since the mid-1990s, scientists have been trying to synthesize several of Vassourinha's phytochemicals, including SDB, for mainstream use by the pharmaceutical industry.

Geranylgeranyl diphosphate synthase (GGPPS) was isolated from the diterpene-producing plant *Scoparia dulcis*, have been isolated using the homology-based polymerase chain reaction (PCR) method. The open reading frames (ORF) of the GGPPS gene from *S. dulcis* encodes a protein of 351 amino acid residues.\[81\]

*Praveen et al. (2009)\[82\] reported that the petroleum ether, diethyl ether and methanol extract of *S. dulcis* possesses potential hepatoprotective activity, which may be attributed to its free radical scavenging potential, due to the terpenoid constituents.*

*Mondal et al. (2009)\[83\] found Amino-n-butyric acid, aspartic acid, glutamic acid, methionine, phenylalanine and praline were the major amino acids found in the various pollen. Total free amino acid content (\%) \(\mu\)mol/mg dry wt. of the pollen of*
Scoparia dulcis with standard deviation (sd) was found to be 3.85 sd 0.077 (Amino-n-butyric acid 1.014, Aspartic acid 1.016, Cysteine0.142, Glutamic acid 0.161, Isoleucine 0.044, Methionine 0.056, Phenylalanine 0.083, Proline 1.216, Threonine 0.014 and Tyrosine 0.089).

Scopadulcic acid B (SDB) was produced by immobilizing suspension culture-derived cells of Scoparia dulcis on Luffa sponge matrix. SDB is a diterpine having antiviral and anti-tumor activity.  

According to Brindha et al. (2012) Scoparia dulcis has elemental and neutraceutical value. It contains macronutrients like carbohydrate 1.43 mg/kg, Protein 0.72 mg/kg, Fats 0.03 mg/kg, Energy 5.99 Kcal and micronutrients carbon 4.59%, Nitrogen 1.79%, Phosphorus 0.87%, Potassium 4.28%, Sodium 0.69%, Calcium 5.23%, Magnesium 3.91%, Sulphur 0.52%, Zinc 4.53ppm, Copper 1.29ppm, Iron 56.32ppm, Manganese 12.54ppm, Boron 0.12ppm, Molybdenum 0.16ppm. S. dulcis contain Zinc 4.53ppm, Iron 56.32ppm, Calcium 5.23%, Sodium 0.69%, Magnesium 3.91% and Flavanoids 2.54 mg/kg. So this plant can also be useful for anaemic patients and could act as an antioxidant. The accumulation of fat in the cells leads to injury or cell death, sodium supplement either abolishes or significantly reduces the accumulation of fat and it also completely prevents the myofibre death. Cardioprotective effect of sodium is independent of its hypothermic action. During cardiac hypoxia, increased levels of extracellular magnesium shows cardio protective effects. Decreased Mg resulting due to hypoxic perfusion will lead to Mitochondria KATP channel blocking. Due to the increased Mg content this plant drug can supply magnesium thus prevent KATP channel blocking and could offer cardiac protection. Thus, a moderate percentage of sodium (0.69%) and Magnesium (3.91%) makes it a good dietary supplement for heart patients.

Hayashi et al. (2005) Signal transduction events which are involved in methyl jasmonate (MeJA) enhanced production of the tetracyclic diterpene, scopadulcic acid B (SDB), were investigated in leaf organ cultures of Scoparia dulcis. Pretreatment of leaf organ cultures with Ca²⁺-channel blocker, verapamil, resulted in a dose-dependent inhibition of MeJA enhanced SDB production.
From the aerial parts of *Scoparia dulcis* L. (Scrophulariaceae) grown in Vietnam,\(^{[87]}\) isolated four scopadulane-type diterpenoids (4-7), of which 7 is new and was given the trivial name scopadulcic acid C, together with nine known compounds.

### 1.4.5 REVIEWS OF PHARMACOLOGICAL ACTIVITIES

#### 1.4.5.1 Analgesic Activity

It has been reported that *in-vivo* analgesic activity on 95% ethanol extract of *S. dulcis* has been evaluated for centrally acting analgesic potential using hotplate and peripheral pharmacological actions using acetic acid induced writhing test in mice. The crude extract was found to have significant analgesic activity at dose of 100 & 200 mg/kg BW. This finding supports the use of whole herb of *S. dulcis* in painful conditions acting both centrally and peripherally. It was found that the observed analgesia in *S. dulcis* was demonstrated by the active constituents, Glutionl, a triterpene\(^{[88,89]}\) and Scoparinol, a diterpene\(^{[90]}\) isolated from the plant extract through a peripherally acting mechanism similar to the non-steroidal anti-inflammatory agents, such as indomethacin and diclofenac sodium. Preliminary qualitative phytochemical screening reveals the presence of alkaloids, carbohydrates, glycosides & tannins in *S. dulcis*. Therefore, it is assumed that these compounds may be responsible for the observed analgesic activity. Flavonoids were reported to have a role in analgesic activity primarily by targeting prostaglandins.\(^{[91,92]}\) There are also reports on the role of tannins in anti-nociceptive activity.\(^{[93]}\) Besides, alkaloids are well known for their ability to inhibit pain perception.\(^{[94]}\) The plant extracts of *S. dulcis* exhibited both types of pain inhibition.\(^{[95,96]}\)

#### 1.4.5.2 Anti-cancer Activity

Much of the recent research on *Scoparia dulcis* has centered around one powerful phytochemical called scopadulcic acid B (SDB). In a clinical study in 1993, SDB inhibited the growth of tumors in a test tube and in mice. Since the mid-1990s, scientists have been trying to synthesize several phytochemicals of *S. dulcis*, including SDB, for mainstream use by the pharmaceutical industry. Scopadulcic acid B, a tetracyclic diterpenoid, inhibited the effects of tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) *in vitro* and *in vivo*; SDB inhibited TPA-
enhanced phospholipid synthesis in cultured cells, and also suppressed the promoting effect of TPA on skin tumor formation in mice initiated with 7, 12-dimethylbenz[a]anthracene. The potency of SDB proved to be stronger than that of other natural antitumor-promoting terpenoids, such as glycyrrhetinic acid. One of the chemical constituents is an aphidicolin-like tetracyclic diterpene named scopadulciol (SDC), which was isolated from *S. dulcis*. SDC showed stimulatory effect on antiviral potency of acyclovir (ACV) or ganciclovir (GCV). Such effect of SDC revealed to be exerted by activation of *Herpes simplex* virus thymidine kinase (HSV-1 TK) and, as a result, increase in cellular concentration of the active form of ACV/GCV, i.e. triphosphate of ACV or GCV. On the basis of these experimental results, cancer gene therapy using HSV-1 TK gene and SDC together with ACV/GCV was found to be effective in suppressing the growth of cancer cells.

### 1.4.5.3 Anti-viral Activity

*Scoparia dulcis* was investigated for anti-HSV-2 activity by plaque reduction assay. It was found that water extract of *S. dulcis* was active against HSV-2 with 50% effective dose of 1,190.4 µg/ml and ED$_{50}$ of ethanol extract of *S. dulcis* was 13.8 µg/ml. Ethanol extract of *S. dulcis* showed highest Therapeutic Index (TI) (2.9) against HSV-2G. Moreover, the efficacy of extracts on viral replication at 36 h was demonstrated. Inhibition of HSV-2 yield was found after treating the virus with ethanol extract of *S. dulcis* and water extract with logarithm value reduction of 3.75. Drug combination study of extracts and ACV at 2.95 µg/ml exerted both additive and sub-additive interaction. The ethanol extract of *S. dulcis* was the best effective on HSV-2G using both plaque reduction assay and yield reduction assay.

### 1.4.5.4 Anti-anaemic

Anaemia is the commonest red cell disorder which affects people throughout the world. In tropical and developing countries, 50% or more of pre-school children and pregnant women are moderately or severely anaemic. The disorder may be the result of malnutrition, infection, obstetrical complications resulting in abnormal blood loss or inherited disorders such as haemoglobinopathies or glucose 6-phosphate dehydrogenase. A major feature of infection with trypanosomes is the
development of anaemia. The effect of *Scoparia dulcis* on *Trypanosoma brucei* induced anaemia was investigated on rabbits. Changes in packed cell volume (PCV), haemoglobin (Hb) concentration, red blood cell count (RBC), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC) and mean cell volume (MCV) were monitored. The results obtained indicate that infection with *T. brucei* results in a significant decrease in PCV, Hb concentration and RBC. No significant changes were observed in MCH, MCHC and MCV. However, the severity of observed anaemia was significantly less pronounced in the infected rabbits that were treated with *S. dulcis* when compared with their infected but untreated counterparts. It was concluded that *S. dulcis* therapy may prove useful in the management of *T. brucei* anaemia, and possibly other forms of anaemia. It is possible that *S. dulcis* may possess the ability to preserve and conserve the structural and functional capacity of the red cell membrane or erythropoietic tissues to varying degrees in the face of an offending parasitic infection. Since *T. brucei* infection is associated with massive generation of free radicals [100]. *S. dulcis* has antioxidiant activity.

The herb may possess trypanocidal activity or immuno-stimulating properties that help to put the parasite in check and thus also control the deleterious effect of uncontrolled parasite proliferation. The plant has also been used in the management of sickle cell anaemia for decades. The widespread claims of massive boost in haematocrit or PCV and Hb levels in the patients and the apparent amelioration of the frequent and severe crisis associated with the disease was prompted. Progressive anaemia is widely accepted as a cardinal feature of *Trypanosoma brucei* infection. [101, 102]  

1.4.5.5 Hyperlipidaemia

The anti-hyperlipidemic activity carried out by the infection with *Trypanosoma brucei*, resulted in significant increase in plasma total cholesterol, triacylglycerol and low density lipoprotein (LDL)-cholesterol, while the level of high density lipoprotein (HDL)-cholesterol was also significantly reduced. Further, comparative analysis of data revealed that these lesions were significantly less severe in the infected and treated group relative to their untreated counterparts. However, the precise mechanism underlying the plasma lipid modulating effects of the herb is still a matter of
speculations. There were significant and progressive increases in plasma triacylglycerol, total cholesterol and LDL cholesterol in infected animals when compared with controls. HDL cholesterol levels were however, significantly lower in infected animals relatively. African trypanosomes are lipid auxotrophs that live in the blood stream of their mammalian host, and exogenous lipids play essential role in the parasite’s cell structure and metabolism. Their requirement for lipoproteins as an essential growth factor is now well established. However, lipoproteins that are devoid of their lipid components are ineffective in maintaining the growth of trypanosomes. These parasites find ready sources of lipids namely cholesterol esters, cholesterol and phospholipids in the plasma lipoproteins, LDL and HDL. Trypanosomes lack ability for the de novo synthesis of fatty acids (myristate being an exception) and yet require lipid for the biosynthesis of glycosylated phosphatidylinositol anchors. The parasite induced hyperlipidaemia is believed to be somewhat related to its compulsory requirement for lipids. At present there is compelling evidence for the existence of a trypanosome lipoprotein scavenger receptor that is believed to facilitate the endocytosis of both native and modified lipoproteins including HDL and LDL. There are also indications that altered plasma levels of these lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triacylglycerol) may raise the risk of cardiovascular complications in the mammalian host particularly during chronic infection. It is known that aberrations in the levels of plasma lipids and lipoprotein contribute significantly to the aetiology of arteriosclerosis and associated cardiovascular disorders (infection with Trypanosoma brucei) is accompanied by a mixed type hyperlipidaemia characterized by abnormal plasma lipid and lipoprotein levels. Total cholesterol, LDL cholesterol and triacylglycerol are highly elevated while the HDL: total cholesterol and HDL: LDL cholesterol ratios are depressed in infected animals relative to control. The level of total cholesterol, LDL cholesterol and triacylglycerol in treated animals were significantly lower relative to the infected but untreated group. Furthermore, the parasite induced decrease in HDL cholesterol was also significantly resisted in the treated group, thus enhancing the HDL: total cholesterol and the HDL: LDL ratios. This phenomenon favors a reduction in cardiovascular risk. While the exact mechanism by which S. dulcis achieves this feat is not immediately apparent, it seems...
logical to speculate that the putative mechanism may revolve around reduction in parasite load or the control of the induced dyslipidaemia by means that are independent of any possible trypanocidal activity of *S. dulcis*. [112]

### 1.4.5.6 Reproductive problems

Anti-tumour promoting compounds and antiviral agents were found in *Scoparia dulcis*. It also has antimicrobial and antifungal effects as well as anti-hyperlipidemic action in normal and experimental diabetic rats in addition to its anti-diabetic activity. [113] Hispanic prayers are used in Latin America for healing and against mal yeux. These Spanish-romanic prayers, like the 'oracion' prayer are used during 'santowah' (santigual). The ceremony includes *Scoparia dulcis* which is used to sprinkle holy water (S. Moodie-Kublalsingh, Institute of Languages, University of The West Indies, pers. comm. August, 2000). These prayers (magic rather than religion) are said to have come to the New World with the conquistadors. *S. dulcis* leaves are also used for prostate problem. [114]

### 1.4.5.7 Immunosuppressant Activity [115]

The result obtained showed that infection resulted in an initial rise in both total white blood cells (WBC) and the absolute number of circulating lymphocytes followed by a progressive decrease in total WBC and all WBC subtypes namely; lymphocytes, monocytes and granulocytes, although the percentage of lymphocytes (lymphocytes expressed as percentage of total WBC) remained consistently higher than normal throughout the study period. These changes are consistent with the development of trypanosome-induced immunosuppression in their mammalian host. Treatment with *S. dulcis* at a daily oral dose of 25 mg/Kg BW significantly reduced the severity of the observed lesions when compared with untreated infected animals. Thus the herb demonstrates significant potency in protecting against the parasite induced decrease in the population of immunologically active cells.

### 1.4.5.8 Hepatoprotective Activity

The aqueous extract of *Scoparia dulcis* at a dose of 0.5 g/kg, p.o., significantly prevents the CCL4 induced prolongation of pentobarbitone sleep time, indicating the
cytochrome P₄₅₀ protection activity. However, when treated alone, the extract (0.5 g/kg, p.o.) shows a significant prolongation of pentobarbitone sleep time, indicating the intrinsic cytochrome P₄₅₀ inhibition activity. In addition, the extract shows neither stimulant nor depressant effect on the CNS, as evident from locomotor activity test. The results indicated that, the aqueous extract of *S. dulcis* at an oral dose of 0.5 g/kg, p.o., showed a significant protective effect against CCl₄ induced cytochrome P₄₅₀ damage and also show a significant intrinsic cytochrome P₄₅₀ inhibition activity.

1.4.5.9 Brain Antioxidant Status and Lipid Peroxidation

The brain antioxidant status and lipid peroxidation was monitored by using aqueous extract of *Scoparia dulcis* and a significant increase in the activities of plasma insulin, superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione was observed in brain on treatment with 200 mg/kg body weight of *S. dulcis* aqueous extract (SPEt) and glibenclamide for 6 weeks. Both the treated groups showed significant decrease in thiobarbituric acid reactive substances (TBARS) and hydroperoxides formation in brain, suggesting its role in protection against lipid peroxidation induced membrane damage.

1.4.5.10 Mineralization of Urinary Stone Forming Minerals

Four experimental models namely ‘simultaneous flow static model’ (SSM), ‘simultaneous flow dynamic model’ (SDM), ‘reservoir static model’ (RSM) and ‘reservoir dynamic model’ (RDM) were designed. The inhibition of mineralization of urinary stone forming minerals by medicinal plant *S. dulcis* was investigated along with other plants. The inhibition was studied. Increased intake of fruits juice and seed extract of the plants would be helpful in urinary stone prophylaxis. The fruit juice and seed extract of *S. dulcis* is moderate to good inhibitor of calcium oxalate, calcium carbonate and calcium phosphate mineralization. Sequestering of this insoluble calcium salts by the fruit juice might be due to effective single or mixed ligand chelation by the hydroxyl acids present in them. The hydroxyl acids are expected to form metal ion complexes with calcium. The presence of hydroxyl acids in urine may decrease the amount of ionized calcium available for calcium oxalate precipitate. Relatively poor inhibition of mineralization of calcium
oxalate, calcium phosphate and calcium carbonate precipitation by leaves extracts might be due to a higher pK value of carbonic acid leading to replacement and precipitation of calcium salts of inhibitors rather than soluble mixed chelation. Calcium oxalate is a stubborn constituent of urinary calculi being highly insoluble. It has very poor solubility in the leaves extract as such. However, if the fruit juices are present in the milieu before the formation of calcium oxalate, they may prevent the precipitation of the latter by exerting the specificity of their inhibitor towards calcium ions. Whereas calcium oxalate mineralization is most effective in all the plants. The calcium phosphate mineralization is moderate in all the plants.

1.4.5.11 On Tissue Antioxidant Defense System

The possible antioxidant property of aqueous extract of \textit{Scoparia dulcis} was tested in rats exposed to cadmium. Different group of animals were treated with CdCl$_2$ alone or in combination with graded levels of \textit{S. dulcis} (i.e. 250, 500 and 1000 mg/kg BW, respectively). Cadmium, a known prooxidant was administered subcutaneously (3 mg /kg BW), once a week, for two weeks. The required dose of aqueous extract of \textit{S. dulcis} was administered daily for 2 weeks by gavage. The results showed that relative to controls, cadmium significantly reduced superoxide dismutase activity while significantly increasing catalase activity and malondialdehyde (MDA) levels in the liver and kidney. However, no significant effect was observed in the antioxidant enzyme activities and MDA levels in the heart. The dose of aqueous extract of \textit{S. dulcis} 1000 mg/kg BW, like cadmium when administered alone, exhibited a prooxidant effect but when co-administered with cadmium, the high dose of \textit{S. dulcis} effectively restored the antioxidant enzyme activities in the kidney and liver to levels that are not statistically different from the control. These observations showed that aqueous extract of \textit{S. dulcis} possesses significant antioxidant activity, sufficient to mitigate against free radical induced oxidative stress in experimental cadmium intoxication in the rat.

1.4.5.12 Traditional Anti-diabetic Activity

Oxidative stress is implicated in the pathogenesis of diabetic complications. The experiments were performed on normal and experimental male Wistar rats.
treated with *Scoparia dulcis* plant extract (SPEt). The effect of SPEt was tested on streptozotocin (STZ) treated rat insulinoma cell lines (RINm5Fcells) and isolated islets in vitro. Administration of an aqueous extract of *Scoparia dulcis* by intragastric intubation (p.o.) at a dose of 200 mg/kg body weight significantly decreased the blood glucose and lipid peroxidative marker thiobarbituric acid reactive substances (TBARS) with significant increase in the activities of plasma insulin, pancreatic superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH) in streptozotocin diabetic rats at the end of 15 days treatment. Streptozotocin at a dose of 10 g/ml evoked 6-fold stimulation of insulin secretion from isolated islets indicating its insulin secretagogue activity. The extract markedly reduced the STZ-induced lipid peroxidation in RINm5F cells. Further, SPEt protected STZ-mediated cytotoxicity and nitric oxide (NO) production in RINm5F cells. Treatment of RINm5F cells with 5mMSTZ and 10 g of SPEt completely abrogated apoptosis induced by STZ, suggesting the involvement of oxidative stress. Flow cytometric assessment on the level of intracellular peroxides using fluorescent probe 2′7′-dichlorofluorescein diacetate (DCF-DA) confirmed that STZ (46%) induced an intracellular oxidative stress in RINm5F cells, which was suppressed by SPEt (21%). In addition, SPEt also reduced (33%) the STZ-induced apoptosis (72%) in RINm5F cells indicating the mode of protection of SPEt on RIN m5Fcells, islets, and pancreatic cell mass (histopathological observations). Present study thus confirms antihyperglycemic effect of SPEt and also demonstrated the consistently strong antioxidant properties of *Scoparia dulcis* used in the traditional medicine.

### 1.4.5.13 Wound healing Activity

Leaves are the most frequently utilized plant part and most herbal remedies were prepared as paste and applied externally; in some cases medicinal preparations were also administered orally. *Scoparia dulcis* is reported [123] to have specific wound healing compounds.

### 1.4.5.14 Anti-malarial Activity

Antimalarial activity of plant has been linked to a range of compounds including anthroquinones, berberine, flavonoids, limonoids, naphthquinones, sesquiterpenes,
quassinoids, indol and quinolone alkaloids. *Scoparia dulcis* is used \(^{124}\) to treat malaria in Colombia and Venezuela.

### 1.4.5.15 Antimicrobial Activity

In Assam, Sikkim and Arunachal Pradesh, the fermented beverages are commonly prepared by using plants and cereals. From the study conducted in the 10 districts, it was evident that all tribes use some plants for starter preparation; however, the type of plant varies from tribe to tribe and district to district. Most of the people are illiterate or not much educated, even though they know the antimicrobial activity of these plants. The detail study and uses of these plants clearly indicate that the presence of these plant materials and their bactericidal activity are mainly responsible for protecting and preserving starter cultures since traditional system of fermentation normally operates in unhygienic condition which sometimes contaminates the system and cause toxication of drinks. But due to the presence of antimicrobial chemical principles of this plant or plant parts, they are able to continue such practice for generations without much decline in the characteristics of microorganisms involved in fermentation. In the preparation of starters of fermentation they use some of the wild plants as antimicrobials without knowing the actual role of these plants in fermentation. They say that either yeast is formed from these plants or these plants are responsible for the yeast’s action in fermentation. All these plants are identified as medicinally important and possess antimicrobial activities.

The whole plant of *Scoparia dulcis* is grinded and made into a paste. Soaked rice is grinded and mixed with the plant paste to use as a starter. \(^{125}\)

### 1.4.5.16 Pro blood clotting activity

Traditional Physicians in rural down south areas apply crushed *S. dulcis* plant on cuts and bruises to stop bleeding. *S. dulcis* may also have Rakta Sthambhana property. The study on effect of decoction (water extract) of *S. dulcis* on blood clotting time in rats was carried out. \(^{126}\) Nine groups of male and female rats (n= 6/gp) were investigated. The group treated with water extract of *S. dulcis* showed significant reduction of clotting time on days 2 and 7. In the group treated with vitamin-K showed reduction
in clotting time on day 7. Thus, it was concluded that *S. dulcis* has pro blood clotting activity and this was faster than vitamin-K.

**1.4.5.17 Inhibition of Gastric acid secretion**

The freeze-dried aqueous extract (AE) from the aerial parts of *Scoparia dulcis* was tested for its effects on experimental gastric hypersecretion and ulcer in rodents. The result pharmacologically validates the popular use of *Scoparia dulcis* in gastric disturbances.

**1.4.5.18 In the Management of Sickle Cell Anaemia**

The use of *Scoparia dulcis* in the management of sickle cell disease by one woman for over two decades and the efficacy of the plant in the management of sickle cell disease was speculated. Therefore, they used *Trypanosome brucei* to investigate the effect of the plant on hematological and biochemical indices due to lack of animal models for assessing the effectiveness of the plant extract in sickle cell disease monitoring. Some researchers have argued in favor of nutrition in the management of sickle cell disease. Oxidative damage to cells is believed to be responsible for activation of KCL-cotransport in sickled erythrocytes. The sickle cell erythrocytes are fragile and dehydrated and it is important that minerals and anti-oxidants are constantly supplied to maintain hydration and membrane integrity. Therefore many tropical plants have been investigated for their micronutrients and anti-oxidative properties. Some of the plants examined so far include *S. dulcis* and some other plants.

**1.4.5.19 Ocular Diseases**

This review explains the herbal drugs used in treatment of ocular diseases and it provide a platform for the researchers to develop more efficient new herbal formulations. *Scoparia dulcis* flower is used in case of Conjunctivitis.
1.5 REFERENCES


10. www.medicinenet.com/high_blood_pressure/article.htm#toc1bp dt.10.01.2012


34. http://arthritis-research.com/content/11/2/R59. dt. 09/02/12

35. naturactiva.net/articles/benefits_shea_butter.doc .dt. 09/02/12


38. http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.108.769554/D C1dt. 15.02.2012


43. http://www.znaturforsch.com/ac/v59c/s59c0177.pdf. 09/02/12


53. www.chemblink.com/products/559-74-0.htm. dt. 09/02/12


58. www.tradingchem.com/Ifflaionic_acid/6805-19-2.html. dt. 09/02/12


62. en.wikipedia.org/wiki/Luteolin. dt. 09/02/12


70. www.selleckchem.com/products/Stigasterol(Stigasterin).html. Dt. 09/02/12
77. en.wikipedia.org/wiki/Vitexin. dt. 09/02/12


