INTRODUCTION

Natural products once served humankind as the source of all drugs, and higher plants provided most of these therapeutic agents. Today, natural products still represent over 50% of all drugs in clinical use, with higher plant-derived natural products representing ca. 25% of the total.
1.1 Introduction

1.1.1 History of Medicinal Plant

Ayurveda is the oldest and widely used system of medicine in the India. Herbal medicine played an important role in the health care system to cure the diseases. The ancient civilizations of the India, China and Africa provide written evidence of natural sources to heal the disease. The Sumerian clay tablet (first documentary evidence before 4000 years) employed in the treatment of various diseases, cuneiform clay tablet from Mesopotamia (2600 B.C.) containing oils from Cupressus sempervirens (Cypress) and Commiphora species (Myrrh) which are still used today to treat coughs, colds and inflammation (Cragg and Newman, 2005). Ebeess papyrees (2900 B.C.), an Egyptian pharmaceutical record, documented over 700 plant-based drugs ranging from gargles, pills, infusion and ointments. The Chinese Materia Medica (1100 B.C.) (Wu Shi Er Bing Fang, contains 52 prescriptions), Shennong Herbal (~100 B.C., 365 drugs) and the Tang Herbal (659 A.D., 850 drugs) are documented records of the uses of natural products. The Greek physician, Dioscorides (100 A.D.), recorded the collection, storage and the uses of medicinal herbs, whilst the Greek philosopher and natural scientist, Theophrastus (300 B.C.) dealt with medicinal herbs.

During the Dark and Middle Ages the monasteries in England, Ireland, France and Germany preserved this Western knowledge whilst the Arabs preserved the Greco-Roman knowledge and expanded the uses of their own resources, together with Chinese and Indian herb subfamilies to the Greco-Roman world. It was the Arabs who were the first to privately own pharmacies (8th century) with Avicenna, a Persian pharmacist, physician, philosopher and poet, contributing much to the sciences of pharmacy and medicine through works such as the Canon Medicine. For instance, mandrake was prescribed for pain relief, turmeric possesses blood clotting properties, the roots of the endive plant were used for treatment of gall bladder disorders, and raw garlic was prescribed for circulatory disorders (Cragg and Newman, 2005). Natural products always help in the maintenance of good health and life. Even today, natural products are becoming increasingly important as alternative medicine and as a source of pharmacotherapeutics for the treatment of many diseases; they are also excellent raw materials from which complex chemical structures with particular biological activity can be isolated.

However, it was not until the nineteenth century that scientists isolated various active chemical constituents from the various medicinal plants. In 1806 Friedrich Sertturner isolated morphine from the Papaver somniferum, atropine from Atropa belladonna, strychnine from Nux vomica, ziconotide from Conus magus and Taxol isolated from Texas barvifolia. According to World Health Organization (WHO), about 80% of the World’s population used medicine obtained from the...
natural sources. In USA (United state of America) 121 drugs used as medicine come from natural sources, 90 of which come either directly or indirectly from plant sources (Benowitz, 1996; Traditional medicine strategy launched, 2002; Handa et al., 2003).

1.1.2 Role of medicinal plant in primary health care

A majority (65 – 80%) of the world’s population, i.e. around 3 billion people still relies on herbal medicines to meet its health needs. The practice continues today because of its biomedical benefits and its place in cultural beliefs in many parts of the world.

India has produced a respectable health care system, i.e. Ayurveda, Unani and Homeopathy, which encompasses the entire spectrum of human health and contributes to the positive health of an individual, but due to certain inimical interferences with the system over the ages, a need has arisen to unify the entire system and codify it. In this context, laying down the standards of Ayurvedic drugs is of paramount importance. This is more so because these days the Ayurvedic drugs are increasingly coming from the industry rather than the Ayurvedic physician compounding them impromptu. Moreover, commercially Ayurvedic drugs can make a debut in international markets, which are looking towards alternative medicines for the cure of ailments to which even modern system has no answer. These ailments include metabolic or degenerative disorders like arthritis, lifestyle induced problems of heart, diabetes and cancer, dementia and age related disorders, immunological disorders and gynecological problems.

Formulation of important guidelines in defining the extent and type of our participation is important while discussing the acceptance of the role of traditional system of medicines and their practitioners in the primary health care. Some of the practices from the traditional system of medicine have already been explored and some require special attention. In this respect the following parameters can be considered. In the history of mankind the progress has been so rapid, that scientific based knowledge has been applied on understanding of drug of natural origin. The ultimate objective of the study of natural products is to contribute to a rational relationship between chemical moiety of naturally occurring drug and biological / therapeutic effects they generated. In the present global scenario, natural medicines are gaining predominance, because they are economical, easily available and relatively free from side effect. The scientist is now emphasizing the study of the traditional plant medicines to discover single biologically active molecule. WHO estimated that 80% of the population of the developing countries relies on traditional medicines, mostly by plant drugs for their primary health care needs (Anon, 1983).

Today different traditional systems of health care rely largely on medicinal plants and much of the world’s population depends on traditional medicine to meet the daily health requirements, especially in developed countries. Use of plant based remedies is also widespread in many industrialized countries and numerous pharmaceuticals are based on or derived from plants. Similarly, cosmetic and other household products may contain plants of medicinal or therapeutic
value. (Magadiet al., 2009). India possesses a rich reservoir of herbal plant wealth considered to be invaluable for remedies of dread ailment such as diabetes, jaundice, asthma, malaria, etc. In India alone about 2,500 plant species are used in the indigenous system of medicine comprising Ayurveda, Unani, Siddha and over 500 plant species are utilized by pharmaceutical industry. The utilization of medicinal plants has increased in recent decades, due to expanding market of herbal drugs in developed countries. (Mazid et al., 2012). Medicinal plants act as a cheap source of raw material their constituents serve as model substances for drug development and their effectiveness can be increased by chemical modification. Since the human system has the necessary means to break them down, biogenic medicine is often more acceptable than synthetic products. Plant extract in crude form exerts a complex effective pharmacological action which explains their superiority over pure isolated products, as synergistic effect of many compounds has been seen.

Regardless of the future of plant-based drugs in the healthcare systems of the more affluent countries of the world, effective western style medicine is neither accessible nor affordable for millions of people worldwide.

- Traditional scholarly systems may be accepted as such.
- Traditional popular practices may be assessed and then accepted.
- The specific areas, which have gained prominence in traditional practices, may be allowed to constitute the specialized components of the total medical care. Therefore, to establish the potentiality of traditional medicine, research needs to be simultaneously conducted on important aspects of these disciplines to meet the requirement of the society where they have to serve.
- To standardize material, method and measures for preparation, preservation, presentation and administration of Ayurveda drugs.
- To give new scientific meaning and significance of the fundamental principles of the system to the extent possible, so that they can be accepted within the scientific framework.
- To rationalize the utility of positive and judicious use of modern scientific methods that pertain to the development of Ayurveda.
- Nevertheless, in doing so the major efforts in this direction may be augmented by introducing the elements of research (Handa et al., 2002)

1.1.3 Medicinal plant and health

The main objectives in research on traditional medicine are follows:

- Understanding the biological mechanism in healthy and disease state.
- Standardization and identifying the biological markers.
- Developing a quantitative understanding of the interaction of drug with key biological system, leading to the more rational design of drugs.
- Understanding the kinetics and dynamic of herbs in our body.
• Developing a drug of low toxicity, reproducible delivery and high specificity for a given pathological state.

1.1.4 National status of herbal medicine

The turnover of herbal medicines in India as over the counter products, ethical and classical formulations and Ayurveda, Unani and Siddha systems of medicine is about $1 billion with a meager export of $80 million. About 80% of the exports to developed countries are of crude drugs and not finished formulations leading to low revenue for the country. The list of medicinal plants exported from India includes Aconitum species (root), Acorus calamus (rhizome), Berberis aristata (root), Cassia augustifolia (leaf and pod), Colchicum luteum (rhizome and seed), Hedychium spicatum (rhizome), Inularacemosa (rhizome), Juglansregia (husk), Junipers communis (fruit), Juniperus macropoda (fruit), Picrorhiza kurrooa (root), Planta goovata (seed and husk), Podophyllum emodi (rhizome), Pinica granatum (flower, root and bark), Rauwolfia serpentine (root), Rheum emodi (rhizome), Saussurea lappa, Ocimum sanctum (Leaves), Centella asiatica (Whole Plant), Emblica officinalis (Fruit), Coriandrum sativum (Leaf and Seed), Asparagus adscendens Tuberous (Root), Terminalia bellerica (Fruit), Cinchona officinalis (Bark), Abelmoschus esculentus (Seed), Tamarindus indica (Fruit), Santalum album (Wood, Volatile oil), Trichosanthes dioica (Fruit), Vitex negundo (Roots, Flower, Fruits and Bark), Aconitum ferox (Root) Alstonia scholaris (Leaves, Bark and Milky Juice), Cocculus cordifolia (Stem, Leaves and Root), Coscinum fenestratum (Stem), Kantak daemiaextensa (Leaves, Root), Piper nigrum (Fruits), Rubia cordifolia (Root), Swertia chirata (Whole herb), Tinospora cardifolia (Stem and Root), Allium sativum (Bulb and Oil), Cassia occidentalis (Leaves, Seeds and Root), Ecliptaerecta (Roots and Leaves), Cuscuta reflexa (Seeds, Stem and Fruits), Achyranthes aspera (Leaves, Seeds and Root), Anacardium occidentale (Fruit, Seed, Bark and Oil), Cannabis sativa (Leaves), Lantana involucrate (Whole Herb), Momordica charantia (Fruit, Leaves and Seeds).

1.2 Diabetes Mellitus

Diabetes was first documented by the Egyptians and is characterized by weight loss and polyuria. However, it was the Greek physician Aerteus who coined the term diabetes mellitus (DM). In Greek, diabetes means “to pass through” and mellitus means “honey”. Diabetes is an important cause of prolonged ill health and premature mortality and claims more lives per year than HIV-AIDS with nearly 1 death every second. Diabetes mellitus (DM) is a condition in which the amount of glucose increases in the blood, because organ properly not utilizes the glucose. DM occurs may be due to hereditary and environmental causes, resulting in abnormally high blood sugar level. The increased level of glucose controlled by the complex interaction of multiple chemicals and hormones in the body including insulin. The role of the insulin in the body-it release after a meal from the pancreas and stimulate the fat cells and muscle to remove the glucose from the blood and stimulate the liver to metabolize glucose, causing the blood sugar level to decrease to normal level. According to the
WHO (World Health Organization), estimation, about 57.2 million adults will be affected in India till year 2025 (King and Herman, 1998; Ahmed et al., 2013). DM is the most common manifestation of metabolic disorder occurs in human due to the high consumption of carbohydrates and lipids (Ramesh and Pugalendi, 2006). The prevalence of Non Insulin Dependent Diabetes Mellitus (NIDDM) is increasing exponentially (Goyal et al., 2010). Its prevalence is more in affluent societies and of general concern. Due to the enormous costs of modern treatment of diabetes in developing countries, the use of medicinal plants has flourished as an alternative for the control and prevention of diabetes complication.

Symptoms for both diabetic conditions may include

- High levels of sugar in the blood
- Unusual thirst
- Frequent urination
- Extreme hunger and loss of weight
- Blurred vision
- Nausea and vomiting
- Extreme weakness and tiredness
- Irritability and mood changes.

### 1.2.1 Epidemiology

According to the WHO estimated around 300 million in the World and 57.2 million adults in India will be affected till the year 2025 (King and Herman, 1998; Ahmed et al., 2013). DM is the most common manifestation of metabolic disorder occurs in human due to the high consumption of carbohydrates and lipids (Ramesh and Pugalendi, 2006). The prevalence of diabetes mellitus is rising and leading to increase in the ratio of the death in the World. The epidemiology of the diabetes mellitus has been linked to the western lifestyle and is uncommon in culture consuming fast food diet.

### 1.2.2 Pathophysiology

Pathophysiology of diabetes remains to be fully understood, experimental evidences suggest the involvement of free radicals in the pathogenesis of diabetes (Matteucci and Giampietro, 2000) and more important in the development of diabetic complications (Oberlay, 1988). Oxygen free radicals such as superoxide (O\(_2^−\)), hydrogen peroxides (H\(_2\)O\(_2\)) and hydroxyl radicals (OH•), are implicated in the pathophysiology of ischemia/reperfusion injury and atherosclerosis (McCord, 1985; Mantha et al., 1993). Oxidation of lipids in plasma lipoproteins and in cellular membranes is associated with the development of vascular disease in diabetes (Morel et al., 1983). Much of the experimental evidence suggests that diabetes and hyperlipidemia alone are not sufficient to provoke vascular disease, but oxidative stress may be an important and independent risk factor in the development of vascular...
disease (Hunt et al., 1990). Free radicals are capable of damaging cellular molecules, DNA, proteins and lipids leading to altered cellular functions. Many recent studies reveal that antioxidants capable of neutralizing free radicals are effective in preventing experimentally induced diabetes in animal models (Naziroglu and Cay, 2001) as well as reducing the severity of diabetic complications (Lipinski, 2001). For the development of diabetic complications, the abnormalities produced in lipids and proteins are the major etiologic factors. In diabetic patients, extra-cellular and long lived proteins, such as elastin, laminin, and collagen are the major targets of free radicals. These proteins are modified to form glycoproteins due to hyperglycemia. The modification of these proteins present in tissues such as lens, vascular wall and basement membranes are associated with the development of complications of diabetes, such as cataracts, micro angiopathy, atherosclerosis and nephropathy (Glugliano et al., 1996). There are also multiple abnormalities of lipoprotein metabolism in very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) in diabetes. Lipid peroxidation is enhanced due to increased oxidative stress in diabetic condition.

1.2.3 Risk Factors Associated With Diabetes Mellitus

Some of the researcher claims that a number of risk factors have been suggested as important contributors to the development of the diabetes mellitus. Researchers don't fully understand why some people develop type 2 diabetes and others don't. It's clear, however, that certain factors increase the risk, including:

1.2.3.1 Weight

The primary risk factor for developing the diabetes is being overweight. During the overweight more fatty tissue developing the resistant cells becomes to insulin.

1.2.3.2 Family history

The risk of type 2 diabetes increases if your parent or sibling has type 2 diabetes.

1.2.3.3 Race

Certain races like Blacks, Hispanics, American Indian, Asian-Americans are more prone to developing the type 2 diabetes as compared to the whites.

1.2.3.4 Age

The risk of developing the diabetes at age 45 causes due to less exercise, weight gain and muscle. But some of the children, young adult and adolescents dramatically prone to type 2 diabetes.

1.2.3.5 Prediabetes

Prediabetes is a condition in which blood sugar level is higher than normal, but not high enough to be classified as diabetes. Left untreated, prediabetes often progresses to type 2 diabetes.

1.2.4 Animal models of diabetes and prevention of diabetes

1.2.4.1 Alloxan induced diabetes

Alloxan (2,4,5,6-tetraoxo hexahydro pyrimidine) was the first agent that was reported to use the induction of the diabetes in the laboratory animals (Dunn and Letchle, 1943). Which selectively
destroys insulin-producing cells in the pancreas (that is beta cells) when administered to rodents and many other animal species.

1.2.4.2 Streptozotocin induced diabetes

STZ (Streptozotocin) is a cytotoxic compound obtained from the soil microbes *Streptomyces achromogenes*. STZ mainly penetrate the β-cells via glucose transporter and break the DNA strand in β-cells, causing the endogenous insulin release (Kumar et al., 2011). Due to breakage of DNA strand leads to amendment of blood sugar level and glucose concentrations in blood. Streptozotocin (STZ) has replaced alloxan as the principal agent used to produce experimental diabetes. This is due to the greater selectivity of β-cells for STZ (Junod et al., 1969) and lower mortality rate seen in STZ-diabetic animals (effective diabetogenic dose of STZ is four or five times less than its lethal dose) (Hoftiezer and Carpenter, 1973).

1.3 Rheumatism Arthritis

The term arthritis explained by the Greek, is swelling of the joints simply resulted in the flow (Rheuma) of fluids, but the word rheumatism was not introduced into the clinical manifestation of chronic inflammation until the sixteenth century by Royal French Physician Guillaume de balloon (Redford, 1980). Chronic inflammation, increased due to imbalance between the anti-inflammatory immunomodulatory pathways and pro-inflammatory. Diaethrodial joints (those with cartilage-capped surfaces, an intervening space filled with viscous fluids and a synovial lined capsule) is the major target for the autoimmune inflammation. The classic example of the immune-mediated joint disease in humans is rheumatoid arthritis. Rheumatic arthritis is a chronic progressive, disabling, chronic multisystem autoimmune disorder (Gomes et al., 2010). It is the most common multisystem disease of unknown causes characterized by pain, swelling, inflammation; tissue damages caused restriction of movement of the limbs. In the inflammation reaction, increased cellularity of synovial tissue and joint damage are the pathological hallmark of RA (Singh et al., 2011). Every year worldwide 1-2% of people were suffering from the RA (Birnbaum et al., 2000; Kwok et al., 2002).

The therapy may include in the treatment of the RA is a non-steroidal anti-inflammatory drugs (NSAIDS) like etoricoxib, ibuprofen, aceclofenac etc., which are not presently through to have important effects on the natural history of the disease, are known to induce significant damage to the upper and lower of the gastrointestinal tract, which is related to the primary biological mechanism of the drugs. Disease modifying anti-rheumatic drugs (DMARDs) like methotrexate, sulphasalazine, leflunomide, hydroxychloroquine, and corticosteroids like prednisolone, methylprednisolone has all been associated with adverse effects. Because of this reason, patients suffering from chronic musculoskeletal disorders are likely to seek alternative methods for symptomatic relief and are amongst the highest users of complementary and alternative medicine.

1.3.1 Epidemiology
RA causes premature mortality, disability and compromised quality of life in the industrialized and developing world. Rheumatoid arthritis is a systemic inflammatory disease which manifests itself in multiple joints of the body. Epidemiological studies of the distribution and determinants of the RA disease in human populations. According to the definition having two fundamental statements: first, the human disease does not happen accidentally and second human disease has causal and preventive factors that can be identified through systematic investigation of different populations in different places or at different times (Fletcher et al., 1988). RA affects the people over the age of 55, 5% of females and 2% of males of total population. But the incidence and severity seen to be less in rural area as compared to the urban area, the onset is frequent during 4-5 decades of life with 80% of patients lie between the ages of 35 and 50 (Redford, 1988). The RA condition development has a high association with HLA-DR$_{4}$ and HLA DR$_{1}$ and familial aggregation (Harisons, 1988). The most commonly affected areas of the RA approximately 80% over the extensor surface of the elbows and fingers (Harsh M, 2000).

1.3.2 Pathophysiology

The causes of the RA are still unknown. Some of the researcher claims that genetic risk factors and some other manifestation like hereditary, environmental and possible infections agent (Mycoplasma, Epstein bar virus, cytomegalo virus, parovirus and rubella virus) are the important etiology of this disease. The genetic studies of the RA have focused on the histo compatibility locus. Some of the researcher claimed that important association between the human leukocyte antigen (HLA) alleles (i.e., HLA-DR$_{4}$ and HLA-DR$_{1}$) and susceptibility to RA (Gregerson et al., 1987; Stastny P, 1978; Nepom et al., 1987). One possibility, of the infection of the articular structures or retention of microbial products in the synovial tissue, which induce an immune response to components of joints by altering its integrity and revealing antigenic peptides. Here micro organism linked because bacteria express reactivity to type II collagen, complete fruend adjuvant and heat shock protein. Recent evidence is that micro organisms might prime the host to cross reactive determinist within joints and similarity between product off certain gram negative bacteria and HLA-DR molecules which supports the possibility. Finally the product of the infecting microorganism might induce the disease, but still the role in the etiology of RA remaining speculative (Harisons, 1998).

1.3.3 Risk Factors Associated With Rheumatoid Arthritis

Some of the researcher claims that a number of risk factors have been suggested as important contributors to the development or progression of RA. Of these, the best studied have been genetics, infectious agents, oral contraceptive medications and smoking. The latest finding in the field of RA suggests that the genetic, environmental or hormonal factors causing the arthritis.

1.3.3.1 Genetics

The hereditary component or genetic factor is important in the etiology of the RA. If patients have a first degree relative with RA, there are chances of getting RA 1.5-3 times higher than someone...
without an RA relative. Genetic studies of the RA focused on the preliminary role of the major
histocompatibility locus in RA.

1.3.3.2 Environmental
Some of the environmental factors play an important role in the development of the RA, such as
exposure to bacteria or a particular diet that may occur naturally in certain locations. Some of the
bacteria and virus infection also trigger to RA. A chemical also affects the immunological mediated
mechanism and non immune mechanisms which involves IgE class of immunoglobulins, e.g.
Rhinitis may occur as an IgE response to toluene, di-isocynate, lead to an antigen / antibody reaction
which manifest itself as asthma or vascular dysfunction which lead to T or B cell abnormality.

1.3.3.3 Hormonal
Some of the researcher claims that the hormones like estrogen and progesterone also caused the RA.
During the pregnancy the level of the estrogen and progesterone was increased and afterwards
decrease the level of the hormones. During the pregnancy, changes in the level of the hormones may
promote the development of the RA in genetically susceptible people. Some of the women having
the irregular menstruation cycle during the age of 20-35 more likely to develop the RA.

1.3.4 Induction of arthritis
Adjuvant disease is generally induced by intracutaneous injection of dead *tuberculous bacilli* in
liquid paraffin (Complete Freund adjuvant) into the foot pad. The ear pinna and a lymphhnode are
alternative sites. Several smaller protein molecules prepared from the cell walls of other bacteria
including *Nocardia, Streptomyces, Streptococcus* and *Lactobacillus*, both bacterial and
peptidoglycon in oil may induce arthritis.

1.3.4.1 CFA induced arthritis
CFA has been shown the number of clinical, chronic and immunological features similar to the
human arthritis. Therefore, this model is used with a relatively high degree of validity for evaluating
agents with potential antiarthritic activity. Swelling in the hind paw is the primary reaction;
characterized feature of the CFA induced arthritis, which persisted for weeks and primary reaction
followed by the development of the arthritic nodules in ear and tails and swelling in the contralateral,
this is called delayed response (secondary reaction).

CFA induced arthritis is induced by injection of 0.05 ml (0.5% w/v) of CFA in the sub
plantar region of the left paw (Purnima et al., 2006).

1.3.4.2 Collagen induced arthritis
Collagen induced arthritis disease, which causes the animals immune system to attack animals own
collagen causing arthritis like response. Once the mice started to chow clinical signs of arthritis as
they are given cannabidiol via a tube pushed down their throat via an injection into the abdomen for
10 days. At the end of the experiment, mice are killed and their hind paws cut off in slices, and
experiment for joint damage as mild, moderate or serve (where cartilage and bone has been destroyed altering the structure the joints).

Medicinal plants are being looked up once again for the treatment of diabetes and arthritis. Major hindrance in amalgamation of herbal medicine in modern medical practices is the lack of scientific and clinical data proving their efficacy and safety. There is a need for conducting clinical research in herbal drugs, developing a simple basis for biological standardization, pharmacological and toxicological evaluation, and developing various animal models for toxicity and safety evaluation. It is also important to establish the active component/s from these plant extracts.