Chapter 1

Introduction
1. INTRODUCTION

Traditional aboriginal knowledge of plants is responsible for most of the medicine and food used in modern society. The exploration of traditional knowledge for cures to common diseases is not only attractive but also overwhelming. There is a chasm between the mountain of traditional knowledge of plant use in society and the handful of plants that supply more than 800 companies producing medicinal plant products worth 4.5 billion every year. Currently there is a phenomenal increase in screening medicinal plant preparations as a safe alternative to conventional medicines (Raghupathy et al., 2007).

Medicinal Plants have been used as healers and health rejuvenators since time immemorial. WHO (World Health Organization) recognizes that medicinal plants play an important role in the health care of about 80 percent of world population in developing countries and depend largely on traditional medicines, of which herbal medicines constitutes the most prominent part. India, because of its vast biodiversity and the potential for commercial exploitation could become a world leader in the supply of raw materials for the pharmaceutical industry (Farnsworth et al., 1991).

Medicinal plants are to be given the status of ‘natural resources’ because their continued availability is essential to sustain one of the world’s oldest medical traditions, a priceless legacy of the Indian people. Millions of rural households have been using medicinal plants sustainable in a self-help mode. A network of around 300 in-situ forest reserves of medicinal plants across the different biogeographic zones and linked to decentralized nurseries and a state level seed center is probably the most effective way for India to maintain and manage the inter and intra specific diversity of medicinal plants and this “network of in-situ gene banks” will also have...
the potential to serve as the backbone for a sustainable cultivation program (Jain, 1978).

Many people have defined medicinal plants in many ways, out of which the accepted definition given by the Agricultural and Natural Resource Development is, “Plants that are recognized by people to have reliable and effective medicinal values, are commonly used in treating and preventing specific ailments and diseases, and play an essential role in health care” (Kokate et al., 2002).

Nature has provided a complete storehouse remedy to cure all ailments of mankind. This is where; nature provides us drugs in the form of herbs, plants and algae to cure the incurable diseases without any side effects (Trease and Evans, 1983). Research on medicinal plants is an important facet of biochemical research in India because of several reasons. Medicinal plants are believed to be an important source of new chemical substances with potential therapeutic effects. The research into plants with alleged folkloric use as pain relievers and anti-inflammatory agents, should therefore be viewed as a fruitful and a logical research strategy in the search for new analgesic and anti-inflammatory drugs (Gupta et al., 2006).

Over 75% of the world population relies mainly on plants and plant extracts for health care and more than 30% of the entire plant species, at one time or another, were used for medicinal purposes (Joy et al., 1998). WHO encourages the inclusion of herbal remedies that have been proven to be efficacious and safe, into primary health care (Amos et al., 2001).

The study of traditional knowledge of plants among tribal communities is an important aspect of ethno botanical research. The tribal peoples throughout the world have developed their own cultures, customs, religious rites, taboos, legends and
myths, medicine, food etc., They are the storehouse of accumulated experience and of knowledge about the native vegetation. The traditional knowledge is an important natural tool to facilitate the development process in cost-effective and sustainable ways. It governs almost all important productive resource sectors and revolves around traditional values of resource use by the people of remote localities (Gadgil et al., 1993). Traditional medical practices are an important part of the tribal health care system in the developing world (Sheldon et al., 1997). During the last few decades there has been an increasing interest in the study of medicinal plants and their indigenous uses in different parts of the world. Documentation of such indigenous knowledge is essential for the conservation and utilization of biological resource (Luoga et al., 2000). In different societies throughout the globe medicinal plants makes the base of the primary health care system and about 85% of traditional medicine are derived from plants (Farnsworth, 1988). In India ethno medicinal investigations have been conducted from various rural and remote areas, where the inhabitants are still dependent on herbal medicines from their primary health care (Gyotsana et al., 2011).

Popular knowledge of plants which can be used by humans is based on thousands of years experience (Rodrigues et al., 2003). It is essential to make the complete inventory of the medicinal components of flora of any country for conservation and sustainable use. The conservation of the threatened and endangered medicinal species in the wild is indispensable (Rahman et al., 2004).

In India, the number of medicinal plants both indigenous and introduced has been estimated to be between 3,000 to 3,500 species of higher plants. The glossary of Indian medicinal plants has listed around 3,000 plants. 2,500 plants have been reported to be used in ethno medicine (Jain, 1991).
Traditionally, medicinal plants have been used to maintain human, veterinary and plant health. There are medical texts that deal with the treatment of cows, horses, elephants and birds. There are also texts on subjects like *Vrksha Ayurveda* and *Krishi Shastra* that deal with the use of plants for controlling pests and treating plant diseases (Jain, 1978).

Plants and plant-derived products are part of the 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 polyherbal formulations was highlighted for health care. Evolution of Ayurveda and plant-based remedies for health care through day-to-day life experiences is a part of the cultural heritage of India. WHO estimates that about 80% of the population living in the developing countries relies on traditional medicine for their primary health care needs. In almost all the traditional systems of medicine, the medicinal plants play a major role and constitute their backbone. Indian *Materia Medica* includes about 2000 drugs of natural origin almost all of which are derived from different traditional systems and folklore practices (Narayana et al., 1998).

It is difficult to get reliable figures for the total number of medicinal plants on earth; according to some estimation, around 35,000–70,000 plant species are being used worldwide in health care systems. According to WHO estimations the populations in developing countries like India (70%), Ruwanda (70%), Uganda
(60%) from Tanzania (60%), Benin (80%) and Ethiopia (90%) extensively use traditional and alternative medicines for health care. Plants and plant-based products are an integrated part of most of the traditional and alternative systems of medicines worldwide. In developed countries like Belgium (31%), USA (42%), Australia (48%), France (49%), Canada (70%), a significant percentage of the population has used traditional and alternative remedies at least once for health care (WHO, 2002). The global market of trade related to medicinal plants is estimated around US $60 billion per year and is growing at the rate of 7% annually with varying shares (Fig. 1) of developed and developing countries. A study reveals that about 42% of the best selling pharmaceutical products in 1997 were biological or natural products or chemical entities derived from natural resources, worth of US $17.5 billion (Mukherjee and Atul, 2006).

![Figure 1: World market of herbal remedies (Mukherjee and Atul, 2006)](image)

The earliest record of human civilization and culture of China, Egypt, Assyria, and Indies valley reveals that the elders and wise men of those times used herbal medicines to treat various diseases. Information regarding these medicinal herbs is available in the old literature, folklore, mythological stories, epic poems, medical treatises and thousand years old manuscripts, palm leaves and copper plates and other
records on these cultures which are preserved even today. The excavation of the Shanidar cave in Iraq in 1963 revealed the grave of a Neanderthal man buried sixty thousand years ago along with many flowers of his time. The plants found in the grave were later identified to having various medicinal properties (Ralph, 1954). One of the earliest records of the use of herbal medicine is that of Chaulmoogra oil from *Hydnocarpus gaertn*, which was known to be effective in the treatment of leprosy. Such a use was recorded in the pharmacopoeia of the Emperor of China between 2730 and 3000 B.C. Similarly, the seeds of the opium poppy (*Papaver somniferum*) and castor seed (*Ricinus communis*) were excavated from some ancient Egyptian tombs, which indicated their use in that part of Africa as far back as 1500 B.C. The records available in “*Ebers papyrus*” also confirm that medicinal plants were used at that time in Egypt (Lanfranco, 1999).

According to medical records, the *Materia Medica* of Hippocrates, who is now referred to as the father of medicine consisted essentially of herbal recipes, some 400 simple remedies having been compiled and described by him. Theophrastus of Athens (370-287 B.C.) was another famous Botanist who produced a number of manuscripts including the famous *historian planetarium*. About 500 plants, mostly cultivated, were described in this manuscript. Pliny, the elder (23-79 A.D.), a Roman naturalist and philosopher, described 1000 plants with their medicinal properties, anatomy and horticultural practices in his book, *Historia Naturalis* (Evans, 2000).

Dioscorides (60 A.D) wrote “*De Materia Medica*” describing 600 plant species of medicinal value from the Mediterranean region. Another manuscript, the Alicia Juliana Codex, was prepared for the daughter of the Byzantine Emperor about 512 A.D. from material originally compiled by Dioscorides (Ralph, 1954 and Evans,
In the middle ages, the writing of Galen (131 A.D.) became popular. Galen is considered today to be the most distinguished physician of antiquity after Hippocrates. He treated diseases essentially by the use of herbs. Allopathic as well as homeopathic systems of medicine today are based on the doctrine explained by Galen (Lanfranco, 1999). The ancient use of plants for healing purposes forms the origin of much of today's modern medicine. Many conventional drugs originate from plant sources: a century ago, most of the few effective drugs were plant based. Examples include aspirin (from willow bark), digoxin (from foxglove), quinine (from cinchona bark), and morphine (from Opium poppy). The development of drugs from plants continues, with drug companies engaged in large-scale pharmaceutical screening of herbs (Tyler et al., 1976). During the last decade, the use of TM (traditional medicine) has expanded globally and has gained popularity. It has not only continued to be used for primary health care of the poor in developing countries, but has also been used in countries where conventional medicine is predominant in the National health care system (Vickers, 1999). It has been confirmed by WHO that herbal medicines serve the health needs of about 80% of the world’s population, especially for millions of people in the vast rural areas of developing countries (WHO, Geneva, 2001).

**Current Status of Medicinal Plants: Global Perspective**

The sources available for understanding the history of use of medicinal plant are archaeological and written documents. The traditions of Japan, India and China were also documented in many early manuscripts and books. In many other parts of the world, the first written records are reported by early travelers who were sent by their respective feudal governments to explore the wealth of the new world. These people included missionaries, explorers, salesmen, researches and later colonial officers (Mazar, 1998).
An early European example is medicinal mushrooms, which were found with the Austrian/Italian ‘iceman’ of the Alps of Otztal (3300 BCE). These mushrooms possessed antibiotic effects against *Mycobacteria* and toxic effects on diverse organisms. Also, scarred cuts on the skin of the iceman might indicate the use of medicinal plants, since the burning of herbs over an incision on the skin was a frequent practice in many ancient European cultures. Hippocrates, a Greek medical doctor (ca. 460-375 BC) was the first of a series of authors who produced the so-called *Corpus Hippocraticum* (a collection of works on medicinal practice) (Capasso, 1998).

The oldest form of traditional Asian medicine is *Ayurveda* and is considered to be the origin of systemized medicine. The term ‘*Ayurveda*’ comes from *ayur* meaning ‘life’ and *veda* meaning ‘knowledge’ and is a later addition to Hindu sacred writing from 1200 BC called the *Artharva-veda*. The first school to teach Ayurvedic medicine was at the University of Banaras in 500 BC and the great *Samhita* was written (http://en.wikipedia.org/wiki/Ayurveda).

The oldest written information on the European-Arabic traditions comes from the Sumerians and Akkadians of Mesopotamia. The Egyptians documented their knowledge (including medicinal and pharmaceutical) on papyrus, which is paper made from *Cyperus aquaticus*, an aquatic sedge.

Greek medicine has been the focus of historical pharmaceutical research for many decades. The Greek scholar Pedanius Dioscorides from Anarzabos (1 BC) is considered to be the ‘father of [Western] medicine’. His works were a doctrine governing pharmaceutical and medicinal practice for more than 1500 years, and which were heavily influenced by European Pharmacy.
In the 16th century the first systematic treatise on (herbal) drugs using a scientific method was produced. The Ben Cao Gang Mu (‘Drugs’ by Li Shizen, 1518 – 1593) contains information about more than 1892 drugs.

Jamu, the Indonesian traditional medicine and Kampo, the traditional Japanese medicine also finds a special relevance in history. For over 1500 years the classical and most influential book in Europe has been *Discorides De materia medica*.

In the 17th and 18th centuries, knowledge about plant-derived drugs expanded, but attempts to ‘distillate’ the active ingredients from plants were unsuccessful. This later led to the development of a field of research now called natural product chemistry or, specifically for plants, Phytochemistry. Pure chemical entities were isolated and their structures elucidated. Some were then developed into medicines or chemically modified for medicinal use and include compounds such as Morphine (1804), Quinine (1820), Salicin (1838), Atropine (1833), Caffeine (1821), Coniine (1826), Emetine (1817) etc. Also, early in the 19th Century, the term ‘Pharmacognosy’ was coined by the Austrian professor Johann Adam Schmidt (1759 – 1809).

**The 20th century**

One of the most important events that influenced the use of medicinal plants in the Western work in the last century was the serendipitous discovery of the antibacterial properties of fungal metabolites such as benzylpencillin, by Florey and Fleming in 1928 at St Mary’s Hospital (London). These natural products changed the perception and use of plant – derived metabolites as medicines by both scientists and the public. Another important development came with the advent of synthetic chemistry in the field of pharmacy.
The latter part of the 20th century saw rapid expansion in knowledge of secondary natural products, their biosynthesis and biological and pharmacological effects. There is now a better understanding of the genetic basis of the reactions that give rise to such compounds as well as the biochemical (and in many cases genetic) basis of many important illnesses. This opened up new opportunities and avenues for drug development.

The practice of traditional medicine (TM) is widespread throughout Asia including China, India, Japan, Pakistan, Srilanka, and Thailand. In Japan, herbal medicinal preparations are more in demand than mainstream pharmaceutical products. 60 to 70% of allopathic doctors in Japan prescribe TM for their patients. In Malaysia, traditional forms of Malay, Chinese and Indian medicine are used extensively. China is the leading country for incorporating traditional herbal medicine into a modern health care system and TM accounts for around 40% of all health care delivered and is used to treat roughly 200 million patients annually. In Canada, it is estimated that a total of US$ 2.4 billion was spent in 1997 on alternative medicine (Der et al., 2000). In 1999 among the 25 best selling drugs in the world, 30% came from natural products (WHO, Geneva, 2001).

Many people in the US are turning to herbal medicine to treat their illnesses. It has been estimated that up to 50% of the prescription presently dispensed in the US may contain one or more natural product drugs (Ernst, 1999). Over 20,000 herbal and other natural products are available in the United States (Douglas, 2001; Miller et al., 2000). In Europe, some 1,500 species of medicinal and aromatic plants are widely used in Albania, Bulgaria, Croatia, France, Germany, Hungary, Poland, Spain, Turkey, and the United Kingdom (Duke, 1993). Germany and France together represent 39% of the global retail markets (Lanfranco, 1992).
The world market for herbal remedies in 1999 was US$ 19.4 billion, with Europe in the lead (US$ 6.7 billion), followed by Asia (US$ 5.1 billion), North America (US$ 4 billion), Japan (US$ 2.2 billion) and the rest of the world (US$ 1.4 billion) (Lemma, 1992). In Europe, Germany has the largest market (US$ 3.5 billion) followed by France (US$ 1.8 billion) and Italy (0.7 billion) (Roufogalis, 1999).

**Current Status of Medicinal Plants: Indian Perspective**

India has one of the oldest, richest and diverse cultural heritages associated with the use of medicinal plants. Even today, there exists around a million traditional, village based carriers of herbal medicine traditions in the form of traditional birth attendants, bone setters, herbal healers and wandering monks who use hundreds of ecosystem specific bio-resources. Complementing the village based carriers, there are more than 5,00,000 licensed registered medical practitioners of the codified systems of Indian medicine like Ayurveda, Siddha, Unani and the Swarigpa (Tibetan) systems of medicine (Savithramma, 2006).

In this context, the contributions of Indians, Egyptians, Chinese, Greeks and Arabs are noteworthy. The Aryans of the Indus Valley wrote three treatises, viz., the Rigveda (2000 B.C.), Atharva veda (2000-1000 B.C.) and Ayurveda (1000-600 B.C.). Ayurveda is the name of some specific single text that was written at a particular point of time rather than an entire science of health care.

*Nuonova Receptro* was published in France in 1408 A.D. Later, after about 50 years, pharmacopoeias in other countries made their appearances. We were well aware of the rich knowledge and tradition of the use of medicinal plants in India. One of the earliest treatises of Indian medicine, “Charaka Samhita” (1000 B.C.) mentions the use of 2000 vegetable herbs for medicinal use (AYUSH, 2006). M.S Valiathan,
the renowned cardiologist published the book, “Legacy of Charaka”, which is an English version of the *Samhita* (Sanskrit: collection) composed by Charaka, the founder of Ayurveda.

India has a rich biodiversity with more than 2, 50,000 Angiosperms and a few Gymnosperms, out of which more than 50,000 species are reported to have medicinal values. Of the 2, 50,000 higher plant species on earth, more than 80,000 are medicinal. India is one of the world’s 12 biodiversity centers with the presence of over 45,000 different plant species. India’s diversity is unmatched due to the presence of different agro-climate zones, 10 vegetation zones, 25 biotic provinces and 426 biomes (habitats of specific species). Of these, about 15,000-20,000 plants have good medicinal value. However, only 7000-7500 species are used for their medicinal values by traditional communities (Joy *et al.*, 2001).

It has been estimated that only 10% of the organic constituents in the plant kingdom have been isolated and characterized. Not all the chemical compounds elaborated by plants are of equal interest to the pharmacognosist. The “active principles” have medicinal properties, which manifest themselves in subtler and less dramatic ways than the poisonous plants (Trease and Evans, 2004).

The importance of medicinal plants in traditional health care, providing clues to new areas of drug research and biodiversity conservation is now well recognized.

**Phytochemicals**

Phytochemicals, chemical compounds that occur naturally in plants (Phyto means "plant" in Greek). Phytochemicals have been used as drugs for centuries. For example, Hippocrates may have prescribed willow tree leaves to abate fever. Salicin,
having anti-inflammatory and pain-relieving properties, was originally extracted from the bark of the white willow tree and later synthetically produced became the staple over-the-counter drug aspirin. There is evidence from laboratory studies that phytochemicals in fruits and vegetables may reduce the risk of cancer, possibly due to dietary fibers, polyphenols, antioxidants and anti-inflammatory effects. An important cancer drug, Taxol (paclitaxel), is a phytochemical initially extracted and purified from the Pacific yew tree.

**Antioxidants**

Oxygen is a highly reactive molecule that damages living organism by producing reactive oxygen species (ROS). Reactive oxygen species, as well as reactive nitrogen species (RNS), are products of normal cellular metabolism and they are well recognized for playing a dual role as both deleterious and beneficial species, since they can be either harmful or beneficial to living systems (Valko et al., 2004).

Antioxidants are substances or nutrients in our foods which can prevent or slow the oxidative damage to our body. When our body cells use oxygen, they naturally produce free radicals (by-products) which can cause damage. Antioxidants act as "free radical scavengers" and hence prevent and repair damage done by these free radicals. Health problems such as heart disease, muscular degeneration, diabetes, cancer are all contributed by oxidative damage. Antioxidants may also enhance immune defense and therefore lower the risk of infection and diseases. (www.HealthCastle.com)

The role of free radicals (Fig. 2) and tissue damage in diseases such as atherosclerosis, heart failure, neurodegenerative disorders, aging, cancer, diabetes mellitus, hypertension and several other diseases are becoming increasingly
recognized (Flora, 2007). Normally about 5% of the inhaled oxygen is converted to harmful ROS like $\text{O}_2^-$, $\text{H}_2\text{O}_2$, $\cdot\text{OH}$ (Bandyopadhyay et al., 1999). In many inflammatory disorders there is excess activation of phagocytes and production of superoxide ($\text{O}_2^-$) radical which can harm surrounding tissue either by a powerful direct oxidizing action or indirectly as with hydrogen peroxide ($\text{H}_2\text{O}_2$) and hydroxyl radicals ($\cdot\text{OH}$) formed from $\text{O}_2^-$ which initiate lipid peroxidation resulting in membrane destruction (Gillham et al., 1997). The tissue damage then provokes an inflammatory response by the production of mediators and chemotactic factors (Lewis, 1989). The ROS are also known to activate matrix metalloproteinase (e.g. Collagenase) causing increased destruction of tissue example collagen damage seen in various arthritic disorders (Cotran et al., 1994).

Understanding of the efficacy and mechanism for the reaction of the biologically important radicals with natural antioxidants is the first step towards the development of new and future therapeutic agents (Soumyakanti et al., 2007).

Figure 2: The role of antioxidants
Antioxidant supplements or foods rich in medicinal plants may be used to help the human body in reducing oxidative damage by free radicals and active oxygen (Fig. 3) (Flora, 2007). The most effective way to eliminate free radicals which cause the oxidative stress is with the help of antioxidants. Recently, there has been growing interest in natural antioxidants of plant origin because they have greater application in the food industry for increasing the stability and shelf life of food products. Moreover, they also find use as nutraceuticals and phytocuticals as they have significant impact on the status of human health and disease prevention (Ekramul, 2004).

Figure 3: Illustration showing cell protection by antioxidants by neutralizing free radicals (Adapted from http://www.amazing-glutathione.com/what-are-antioxidants.html)

Therefore currently, the research interest is focused on the potential role of antioxidants in the treatment and prevention of the above diseases. The most commonly used antioxidants at present are butylated hydroxyanisole (BHA),
butylated hydroxytoluene (BHT), propyl gallate (PG) and tert-butylhydroquinone (TBHQ). However, they are suspected of being responsible for liver damage and carcinogenesis in laboratory animals (Anagnostopou Lou et al., 2006). Therefore, the development and utilization of more effective antioxidants of plant origin are desired.

**Pain**

Pain has been defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Failure to relieve pain is morally and ethically unacceptable (Michel et al., 2003).

**Inflammation**

Inflammation is a pathophysiological response of living tissue to injuries that leads to the local accumulation of plasmatic fluids and blood cells. Though it is a defense mechanism, the complex events and mediators involved in the anti-inflammatory reaction can induce, maintain, or aggravate many diseases (Sosa et al., 2002).

Inflammation is a normal protective response to tissue injury caused by physical trauma, noxious chemical or microbial agents. It is the body response to inactivate or destroy the invading organisms, to remove irritant and set the stage for tissue repair. It is triggered by the release of chemical mediators from injured tissue and migrating cells (Bhitre et al., 2008).

Inflammation is divided into two basic patterns. Acute inflammation is of relatively short duration, lasting from a few minutes up to a few days, and is characterized by fluid and plasma protein exudation and a predominantly neutrophilic
leukocyte accumulation. Chronic inflammation is of longer duration (days to years) and is typified by the influx of lymphocytes and macrophages with associated vascular proliferation and scarring.

**Acute Inflammation**

Acute Inflammation is the immediate and early response to injury designed to deliver leukocytes to sites of injury. Once there, leukocytes clear any invading microbes and begin the process of breaking down necrotic tissues.

This process has two major components

- Vascular changes: alterations in vessel caliber resulting in increased blood flow (vasodilatation) and structural changes that permit plasma protein to leave the circulation (increased vascular permeability)
- Cellular events: emigration of the leukocytes from microcirculation and accumulation in the focus of injury (cellular recruitment and activation)

The cascade of events in acute inflammation is integrated by local release of chemical mediators. The vascular changes and cell account for three of the five classic local signs of acute inflammation: heat (*calor*), redness (*rubor*) and swelling (*tumor*). The two additional cardinal features of acute inflammation, pain (*dolor*) and loss of function (*function laesa*), occur as consequences of mediator elaboration and leukocyte-mediated damage.

**Chronic inflammation**

Chronic inflammation can be considered to be inflammation of prolonged duration (weeks to months to years) in which active inflammation, tissue injury and healing proceed simultaneously. In contrast to acute inflammation, which is
distinguished by vascular changes, oedema and a largely neutrophilic infiltrate, chronic inflammation is characterized by the following:

- Infiltration with mononuclear ("chronic inflammatory") cells including macrophages, lymphocytes and plasma cells
- Tissue destruction, largely directed by the inflammatory cells
- Repair involving new vessel proliferation (angiogenesis) and fibrosis

Chronic Inflammation arises in the following settings:

- Viral infections: Intracellular infections of any kind typically require lymphocytes (and macrophages) to identify and eradicate infected cells.
- Persistent microbial infections, most characteristically by a selected set of microorganism including *Mycobacteria* (tubercle bacilli), *Treponema pallidum* (causative organism of syphilis), and certain fungi. These organisms are of low direct pathogenicity, but typically they evoke an immune response called delayed hypersensitivity which may culminate in a granulomatous reaction.
- Prolonged exposure to potentially toxic agents: Examples include non-degradable exogenous material such as inhaled particulate silica, which can induce a chronic inflammatory response in the lungs and endogenous agents such as chronically elevated plasma lipid components, which may contribute to atherosclerosis.
- Autoimmune disease, in which an individual develops an immune response of self-antigens and tissue. Because the responsible antigens are in most instances constantly renewed, a self perpetuating immune reaction results (e.g., rheumatoid arthritis or multiple sclerosis).
Arthritis

Arthritis is inflammation of one or more joints. Arthritis involves the breakdown of cartilage. Cartilage normally protects a joint, allowing it to move smoothly. Cartilage also absorbs shock when pressure is placed on the joint, such as when you walk. Without the normal amount of cartilage, the bones rub together, causing pain, swelling (inflammation), and stiffness. The individuals of any age can be affected with Arthritis; the usual age of onset is between 25 and 50 with a peak in the 40s and 50s (Shivanand, 2012).

Arthritis, an inflammation of the joints, is usually chronic disease that results from dysregulation of pro-inflammatory cytokines (e.g. tumor necrosis factor and interleukin-1b) and pro-inflammatory enzymes that mediate the production of prostaglandins (e.g. Cyclo-oxygenase-2, leukotrienes, lipooxygenase), together with the expression of adhesion molecules (Dinesh et al., 2007).

Arthritis mainly affects the highly movable joints. The joints most commonly affected by arthritis are weight bearing joints such as feet, knees, hips, spine and other joints such as finger and thumb joints (Strange, 1996).

Arthritis is due to the wearing down of cartilage, which cushions the ends of the bones which is depicted in Fig.4.
Types of Arthritis: Rheumatoid arthritis, osteoarthritis, septic arthritis, gout, pseudo gout, juvenile idiopathic arthritis, Still’s disease and ankylosing spondylitis.
Rheumatoid arthritis (RA)

RA is a systemic, chronic inflammatory disease affecting multiple tissues but principally attacking the joints to produce a non-suppurative proliferative synovitis that frequently progresses to destroy articular cartilage and underlying bone with resulting disabling arthritis. When extra-articular involvement develops— for example, of the skin, heart, blood vessels, muscles and lungs—RA may resemble scleroderma. RA is a very common condition, with a prevalence of approximately 1%; it is three to five times more common in women than in men. The peak incidence is in the second to fourth decades of life, but no age is immune (Kumar et al., 2004).

Morphology (Kumar et al., 2004)

Rheumatoid arthritis causes a broad spectrum of morphological alteration; the most severe occurs in the joints. RA typically present as symmetric arthritis, principally affecting the small joints of the hands, feet, ankles, knees, wrists, elbows and shoulders. Classically, the proximal interphalangeal and metacarpophalangeal joints are affected. Histologically, the affected joints show chronic synovitis, characterized by:

- Synovial cell hyperplasia and proliferation.
- Dense perivascular inflammatory cell infiltrates in the synovium composed of CD4+ T cells, plasma cells and macrophages.
- Increased vascularity due to angiogenesis.
- Neutrophils and aggregates of organizing fibrin on the synovial surface and in the joint space.
- Increased osteoclast activity in the underlying bone leading to synovial penetration and bone erosion. The classic appearance is that of a pannus,
formed by proliferating synovial lining cells admixed with inflammatory cells, granulation tissue and fibrous connective tissue; the overgrowth of this tissue is so exuberant that the usually thin, smooth synovial membrane is transformed into lush, edematous, frondlike (villous) projections. With the full-blown inflammatory joint involvement, periarticular soft tissue oedema usually develops, classically manifested first by fusiform swelling of the proximal interphalangeal joints. With progression of the disease, the articular cartilage subjacent to the pannus is eroded and, in time, virtually destroyed. The subarticular bone may also be attacked and eroded. Eventually the pannus fills the joint space, and subsequent fibrosis and calcification may cause permanent ankylosis.

**Pathogenesis** (Kumar et al., 2004)

There is a genetic predisposition to RA and that the joint inflammation is immunologically mediated; however, the initiating agent/s and the precise interplay between genetic and environmental factors are not yet understood.

It is proposed that the disease is initiated in a genetically predisposed individual by activation of helper T cells responding to some arthritogenic agent, possibly microbial. In turn, the activated CD4+ cells produce cytokines that will:

- Activate macrophages and other cells in the joint space, releasing degradative enzymes and other factors that perpetuate inflammation and
- Activate B-cells, resulting in the production of antibodies, some of which are directed against self-constituents. The rheumatoid synovium is rich in both lymphocyte and macrophage-derived cytokines. The activity of these cytokines accounts for many features of rheumatoid synovitis; not only are they
proinflammatory, some, such as IL-1/TNF and TGF-α, cause synovial cell and fibroblast proliferation. They also stimulate synovial cell and chondrocyte secretion of proteolytic and matrix-degrading enzymes.

![Figure 6: Pathogenesis of rheumatoid arthritis (Kumar et al., 2004)](image)

**Cytokines**

Cytokines are low molecular weight polypeptides (typically 10 to 40 kDa) that are secreted by lymphocytes as well as by effector cells, epithelial cells and mesenchymal cells.

Cytokines are produced during immune and inflammatory responses: their secretion is typically transient and tightly regulated. Many cell types produce multiple cytokines and the effects tend to be pleiotropic (different cells are affected differently by the same cytokine)
Cytokines may be roughly grouped into five classes based on their actions or target cells.

- Cytokines that regulate lymphocyte function such as activation, growth and differentiation (e.g., IL-2, which stimulates proliferation and transforming growth factor β, which inhibits lymphocyte growth).
- Cytokines involved in innate immunity, that is, the primary response to injurious stimuli. These include two major inflammatory Cytokines, TNF and IL-1.
- Cytokines that activate inflammatory cells particularly macrophages during cell–mediated immune response, such as interferons –γ (INF-γ) and IL-12.
- Chemokines that have chemotactic activity for various leukocytes.
- Cytokines that stimulate hematopoiesis, including granulocyte–monocyte colony–stimulating factor (GM-CSF) and IL-3.

**Interleukin 1 and Tumor Necrosis Factor**

Although, historically associated with cellular immune responses, various Cytokines, in particular IL-1 and TNF, have additional effects that are important in inflammatory responses (Fig. 7). Both IL-1 and TNF are produced by activated macrophages (IL-1 can also be synthesized by other cell types), and secretion is stimulated by endotoxin, immune complexes, toxins, physical injury, or a variety of inflammatory mediators. IL-1 and TNF induce endothelial activation with increased expression of adhesion molecules, secretion of additional cytokines and growth factors, production of eicosanoids and nitric oxide (NO), increased endothelial thrombogenicity. TNF also causes aggression and activation of neutrophils and the
release of proteolytic enzymes from mesenchymal cells, thus contributing to tissue damage. Both cytokines activate tissue fibroblasts, resulting in increased proliferation and production of extracellular matrix. IL-1 and TNF also induce the systemic acute-phase responses typically associated with infection or injury.

Figure 7: Role of cytokines in rheumatoid arthritis (McCachren et al., 1990; Gravallese et al., 1991)

Conventional Approaches

There are four main groups of drugs used to treat arthritis: Pain killers (analgesics), non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids (steroids) (Sunetra et al., 2010).

Drugs that are currently used for the management of pain are opioids or non-opioids and that for inflammatory conditions are non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. All these drugs carry potential toxic effects. One study suggests that the risk of gastrointestinal bleeding was significantly associated
with acute use of non-steroidal anti-inflammatory drugs (NSAIDs) like regular-dose aspirin, diclofenac, ketorolac, naproxen or nimesulide. Piroxicam increased the risk of bleeding in both acute and chronic therapy (Pilotto, et al., 2003). Opioids are the commonly used drugs for the management of acute postoperative pain (David et al., 2003).

Today, a much more aggressive treatment approach is advocated for people with RA, with prescription of non-biologic DMARDs within three months of diagnosis to reduce disease activity and prevent joint deformity. (Guidelines for the management of rheumatoid arthritis, 2002)

The 2008 guidelines recommend that treatment with non-biologic and biologic therapies should be accompanied by non-medical interventions including physical and occupational therapy and anti-inflammatory pharmacological interventions (e.g., treatment with NSAIDs, intraarticular and oral glucocorticoids) (Saag et al., 2008).

Tenoxicam (TN) (Gupta et al., 2006) is a thienothiazine derivative of the oxicam class of the NSAIDs, which is chemically, 4-Hydroxy-2-methyl-N-2-pyridyl-2 (H) -thieno[2,3-e]-1,2-thiazine-3-carboxamide-1,1-dioxide. TN exhibited potent anti-inflammatory, analgesic, and anti-pyretic activity and is widely prescribed for the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout and nonarticular rheumatic condition (Velpandian et al., 1998; Vavia et al., 1999). Tenoxicam has some side effects when taken orally, viz., epigastric pain, heartburn, nausea, diarrhea, vomiting, peptic ulcer, and hepatic impairment (Perpigana et al., 1994).

Despite considerable progress in the treatment of arthritis by NSAIDs and other drugs, search for newer drugs continues because the existing synthetic drugs
have several limitations. The modern medicine has also started admitting that Ayurveda and herbal medicine, has a lot of positive influence on the treatment of arthritis. A large number of medicinal plants have been tested and found to contain active principles with curative properties against arthritis. Anti-arthritic plants contain a variety of chemical constituents like phenols, coumarins, essential oils, monoterpenes, catechins, quinones, carotinoids, flavanoids, alkaloids, anthocyanins and xanthines (Shah et al., 2006).

**Phytopharmaceutical Approaches**

**Herbal drugs commonly used in the treatment of Rheumatoid arthritis (RA)**

The efficacy of some valuable herbs like Guggul, bhallataka, ginger, Ashwagandha etc., that have a history of human use and their anti-inflammatory or anti-arthritic properties have been evaluated pre-clinically and clinically. Basic scientific research has uncovered the mechanism by which some plants afford their therapeutic effects. Available data suggests that the extracts of most of these herbs or compounds derived from them may provide a safe and effective adjunctive therapeutic approach for the treatment of arthritis.
Table 1: The commonly used herbs for the treatment of Rheumatoid Arthritis (RA)

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Plant name</th>
<th>Family</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td><em>Alpinia galanga</em></td>
<td>Scitaminaceae</td>
<td>Root powder/oral</td>
</tr>
<tr>
<td>02</td>
<td><em>Boerhaavia diffusa</em></td>
<td>Nyctaginaceae</td>
<td>Root powder/oral</td>
</tr>
<tr>
<td>03</td>
<td><em>Cardiospermum helicacabum</em></td>
<td>Sapindaceae</td>
<td>Leaf powder/oral</td>
</tr>
<tr>
<td>04</td>
<td><em>Clerodendrum phlomoides</em></td>
<td>Verbenaceae</td>
<td>Leaf powder/oral</td>
</tr>
<tr>
<td>05</td>
<td><em>Premna integrifolia</em></td>
<td>Verbenaceae</td>
<td>Leaf &amp; root powder/oral</td>
</tr>
<tr>
<td>06</td>
<td><em>Withania somnifera</em></td>
<td>Solanaceae</td>
<td>Root powder/oral</td>
</tr>
<tr>
<td>07</td>
<td><em>Abutilon indicum</em></td>
<td>Malavaceae</td>
<td>Leaf fomentation/external</td>
</tr>
<tr>
<td>08</td>
<td><em>Adasonia digitata</em></td>
<td>Malavaceae</td>
<td>Leaf fomentation/external</td>
</tr>
<tr>
<td>09</td>
<td><em>Anisomeles malabarica</em></td>
<td>Lamiaceae</td>
<td>Leaf fomentation/external</td>
</tr>
<tr>
<td>10</td>
<td><em>Brassica alba</em></td>
<td>Cruciferae</td>
<td>Seed poultice/external</td>
</tr>
<tr>
<td>11</td>
<td><em>Cordoba indica</em></td>
<td>Capparidceae</td>
<td>Leaf poultice/external</td>
</tr>
<tr>
<td>12</td>
<td><em>Calotropis gigantea</em></td>
<td>Asclepiadaceae</td>
<td>Leaf &amp; latex poultice/external</td>
</tr>
<tr>
<td>13</td>
<td><em>Cassia fistula</em></td>
<td>Caesalpinaceae</td>
<td>Fruit poultice/external</td>
</tr>
<tr>
<td>14</td>
<td><em>Erythrina indica</em></td>
<td>Papilionaceae</td>
<td>Leaf poultice/external</td>
</tr>
<tr>
<td>15</td>
<td><em>Jatropha carcass</em></td>
<td>Euphorbiaceae</td>
<td>Seed poultice/external</td>
</tr>
<tr>
<td>16</td>
<td><em>Justicia adhatoda</em></td>
<td>Acanthaceae</td>
<td>Leaf poultice/external</td>
</tr>
<tr>
<td>17</td>
<td><em>Nigella sativa</em></td>
<td>Ranunculaceae</td>
<td>Seed poultice/external</td>
</tr>
<tr>
<td>18</td>
<td><em>Vitex negundo</em></td>
<td>Verbenaceae</td>
<td>Leaf poultice/external</td>
</tr>
<tr>
<td>19</td>
<td><em>Zingiber officinale</em></td>
<td>Scitaminaceae</td>
<td>Root poultice/external</td>
</tr>
<tr>
<td>20</td>
<td><em>Ziziphus jujube</em></td>
<td>Rhamnaceae</td>
<td>Root &amp; bark poultice/external</td>
</tr>
</tbody>
</table>
Fifty medicinal plants belonging to 36 families are identified which have been employed by Kanikkars, the predominant tribal community living in Kalakad-Mundanthurai Tiger Reserve of Western Ghats, Tirunelveli, Tamil Nadu, for the treatment of rheumatism. Plants used by the Kanikkars for the treatment of rheumatism include, *Aloe barbadensis*, *Anisomeles indica*, *Anisomeles malabarica*, *Azadirachta indica*, *Begonia malabarica*, *Cardiospermum helicacabum*, *Datura metel*, *Jatropha gossypifolia*, *Justica adhatoda*, *Leea indica*, *Plumbago zeylanica*, and *Vitex negundo*. The fresh leaves were boiled in coconut oil, water, or neem oil and after cooling, the paste applied to the affected joints to get relief from various forms of inflammations. Sometimes the fresh leaf juice was administered orally to patients suffering from rheumatism. Also other parts of the medicinal plants like roots, flowers, fruits, rhizome, seeds, stem bark etc., were also used (Sutha et al., 2010).

A study conducted by Jyotsana et al., (2011) on the plants used for the treatment of rheumatism by the Bhoxa tribe of district Dehradun, Uttarakhand, India lists 22 plant species belonging to 19 families.

Considerable studies have been carried out on ethnomedical plants; however, only few medicinal plants have attracted the interest of scientists, to investigate them as a remedy for arthritis. The indigenous medicinal plants having anti-arthritic potential are viz., *Alangium salvifolium*, *Alpinia galanga*, *Clerodendrum inermae*, *Bacopa monniera*, *Barringtonia racemosa*, *Cedrus deodar*, *Cleome rutidosperma*, *Cocculus hirsutus*, *Hybanthus enneaspermus*, *Cyperus rotundus*, *Glycine max*, *Merremia tridentate*, *Premna serratifolia*, and *Strychnos potatorum*. *In-vivo* studies were carried out to establish the anti-arthritic and anti-rheumatic efficacy of the above plants (Vivek et al., 2012).