1. Introduction

Arthritis is a chronic, inflammatory, multisystem autoimmune disease which affects almost all age groups of people. Age, gender, dietary habits, consumption of alcohol, hereditary, excess body weight, hormonal factors etc can act as a risk factor for arthritis. There are about hundred types of arthritis; among them rheumatoid arthritis and osteoarthritis are more popular. The disease may explode after pregnancy in women and are highly prone to arthritis when compared to men. Rheumatoid arthritis is a chronic systemic inflammatory disorder that may affect many tissues and organs like skin, blood vessels, heart, lungs and muscles, but primarily attacks the joints producing a non suppurative proliferative and inflammatory synovitis which may lead to the destruction of the articular cartilage and end in the ankylosis of the joints. Though the cause of the rheumatoid arthritis is unknown, it is believed that autoimmunity plays a pivotal role in its chronicity and progression.

At the onset of rheumatoid arthritis, synovium becomes oedematous, thickened and hyperplasic which is caused by the infiltration of synovial stroma by dense perevascular inflammatory cells, \textit{viz.}, B cells and CD4+ helper T cells, plasma cells and macrophages. The perpetuation is mediated by increased vascular permeability as a result of vasodialation and angiogenesis with superficial hemosiderin deposits. This promotes the accumulation of neutrophils in the synovial fluid and along synovial membrane which triggers osteoclastic activity in underlying bone leading to the synovial penetration into the bone causing juxta- articular erosions, subchondrial cysts and osteoporosis which ultimately leads to the pannus formation which grows over the articular cartilage and causes its erosion (Kumar \textit{et al.}, 1998).
The inflammatory process in rheumatoid arthritis is initiated by an immunological trigger (Choy et al., 2001). The inflamed synovium consists of synovial macrophages and fibroblasts where as plasma cells dendritic cells, T lymphocytes and mast cells are found in the sub synovial layer. During synovial proliferation, pannus invade from the joint margins, stimulates the release of matrix metallo proteinases from synovial fibroblasts which mediate cartilage thinning. Chondrocytes mediated destruction and failure of repair mechanisms eventually leads to ankylosis and bone erosion (Kinne et al., 2000; Kumar et al., 1998). Although the etiology of rheumatoid arthritis is not completely known, recent advances in molecular technology have made it possible to identify distinct cell subsets, cell surface markers and cell products that contribute the immune mediated inflammatory responses associated with the disease (Moreland et al., 1999).

Macrophages play a vital role in pathogenesis which are activated by Th1 cytokines such as interferon-γ (IFN-γ), interleukin-12 (IL-12) and interleukin-18 (IL-18) released as a result of the activation of T cells by antigen presenting cells or immune complexes. Activated macrophages in turn releases multiple cytokine and other inflammatory mediators (Choy et al., 2001) which exert autocrine, paracrine and endocrine effects and influence the production of others and regulate cytokine action (Nawroth et al., 1986). Thus an inflammed joint of rheumatoid arthritis patient consists of variety of pro inflammatory cytokines viz., IL-1, TNF-α, IL-6, IL-15, IL-16, IL-17, IL-18, IFN-γ, granulocyte macrophage colony stimulating factor and chemokines such as macrophage inflammatory protein 1-α and monocyte chemo attractant protein-1. Under normal physiological conditions, the actions of pro inflammatory cytokines are in equilibrium with the anti inflammatory cytokines such as IL-4, IL-10, IL-11, and IL-13 and with natural cytokine antagonists such as IL-1 receptor antagonist (IL-1ra), soluble type 2 IL-1 receptor, soluble TNF receptor (sTNF-R1) and IL-18 binding protein. In
arthritic conditions, the balance dangles in favour of the pro inflammatory cytokines (Arend, 2001). It is clear that both IL-1 and TNF-α have an imperative role in the pathogenesis of RA. Arthritogenicity of both cytokines was observed when injected into the joints of experimental animals (Saez-Llorens et al., 1990 & 1991). Apart from this, spontaneous development of arthritis is noted in transgenic mice over expressing either cytokines (Ghivizzani et al., 1997; Niki et al., 2001; Keffer et al., 1991). Furthermore, a spontaneous erosive arthritis is found in IL-1ra knockout mice (Horai et al., 2000). In many animal models of RA, reduction of inflammation and joint destruction was observed as a result of blockade of IL-1 or TNF-α (Bresnihan et al., 1998; Jiang et al., 2000; Cohen et al., 2002; Moreland et al., 1999; Bathon et al., 2000; Maini et al., 1999; Lipsky et al., 2000). The receptors of both IL-1 and TNF-α activate similar intracellular signalling pathways thus the similarity in their biological actions are explained. The Type 1 IL-1 receptor and TNF- receptor (TNF-R) activate a family of adapter proteins called TNF-R associated factors TNFAF-2 and TNFAF-6 by TNF-α and IL-1 respectively (Bradley and Pober, 2001; Inoue et al., 2000; Gravallese et al., 2001).

These tumour necrosis factor receptor associated factors (TRAFs) in turn activates downstream signalling pathways including nuclear factor kB (NF-κB) - mediated transduction mechanisms. Many of the products of NF-κB inducible genes are involved in the inflammatory and immune responses which encode adhesion molecules, cytokines, growth factors, cytokine receptors, immune regulatory molecules and acute phase proteins. Enzymes encoded by NF-κB inducible genes involve in the biosynthesis of inflammatory mediators such as cyclo oxygenase (COX-2) and inducible nitric oxide synthase (iNOS) which are responsible for the production of prostanoids and nitric oxide respectively. COX-2 highly expressed in the rheumatoid synovium where COX-1 expression is almost localized to the synovial lining layer in both rheumatoid and osteo
arthritic cases. Arachidonic acid is released by the action of phospholipase $A_2$ (PLA$_2$) enzymes and is then converted into prostanoids, prostaglandins and thromboxanes through the intermediate COX-1 and 2 and into leukotrienes through the intermediate 5-lipoxygenase enzyme. The intermediate prostaglandin product PGH$_2$ produced by COX-1 and 2 is finally converted into prostaglandin or thromboxane end products by terminal synthase enzymes which exist in several forms. One form may exist constitutively including cytosolic group IV-α PLA2 (cPLA2), COX-1 and cytosolic PGES (cPGES) and are induced in inflammatory conditions following cytokine stimulation including COX-2, microsomal PGES (mPGES) and multiple type of secretory PLA2 (sPLA2) (Katori et al., 1998; Jamal, 1998). Both IL-1 and TNF α up regulate expression of COX-2 and mPGES in rheumatoid synoviocytes leads to over expression of PGE2 which in turn causes several effects that may lead to cartilage erosion and bone resorption by osteoclasts (Lader and Flanagan, 1998; Raisz, 1999; Abramson, 1999).

Nitric Oxide (NO) is another mediator that appears to be more important in cartilage and bone destruction (Lotz, 1999) produced through constitutive and inducible pathways which are responsible for its pathogenic activity. Like COX-2, the transcriptional control of iNOS is regulated by cytokines such as IL-1 and TNF-α as well as other cellular stimuli (Grabowski et al., 1996). The iNOS enzymes catalyses the conversion of L-arginine in the presence of molecular oxygen and co factor NADPH into NO and l-citrulline. NO activates matrix metallo proteinases which inhibits collagen and proteoglycan synthesis by chondrocytes and promotes vasodilation which sequentially leads to fluid and cellular influx into an inflammatory site. When combines with reactive oxygen species, NO produces peroxynitrite which promote chondrocyte apoptosis (Lotz et al., 1999). Once the cartilage has been destroyed, the pannus bridging the opposing
bones forms a fibrous ankylosis which eventually ossifies ultimately results to bony ankylosis (Kumar et al., 1998).

Disease modifying anti rheumatic drugs (DMARDs), the therapeutic agents currently available for the treatment of arthritis are not initially developed for treating RA, but merely reduce the rate of damage to bone and cartilage. Even though DMARDs shows better efficacy when compared with placebo, primarily aim at symptomatic relief rather than a definite cure (Moreland et al., 1997). The most common adverse events reported are liver and bone marrow toxicity (Methotrexate, leflunomide, azathioprine, gold compounds, D-penicillamine), renal toxicity (cyclosporine and parenteral gold salts, D-penicillamine), pneumonitis (Methotrexate), allergic skin reactions (gold compounds), autoimmunity (D-penicillamine, minocycline) and infections (Azathioprine, Cyclosporine A). The understanding of immune pathogenesis of RA paves way to target the immune response pathways using more specific therapies (Moreland et al., 1997). Newer and safer drugs are being searched because of the adverse effects of non steroidal anti inflammatory drugs NSAIDs, disease modifying anti rheumatic drugs (DMARDs) and glucocorticoids.

Recently efforts have been focussed on biological agents which include monoclonal antibodies (Mab) directed against cell surface markers like CD4 or recombinant forms of natural inhibitory molecules such as IL-1(rIL-1RA), TNF(rTNF-R-Fc) for the treatment of osteoarthritis (OA) and Rheumatoid arthritis (RA). Although biological agents reduce inflammation and joint destruction, their long term risks and benefits are not yet clear. Apart from this, their higher costs and the findings that they are not effective universally and severe side effects such as life threatening infections and increased risks of malignancies limit the use of such agents in many populations (Feldman and Steinman, 2005; Arend and Dayer, 1995; Feldman and Maini, 2001; Brown et al., 2002 ; Baghai et al., 2001). Hence, the use of Complementary and Alternative
Medicine (CAM) therapies such as acupuncture and extracts of medicinal herbs is on rise. According to the reports, nearly 60-90% of dissatisfied arthritis patients are likely to look for CAM therapies (Engel and Straus, 2002; Jacobs et al., 1992). This is because of the belief that traditional medicine system around the world including ancient Chinese medicine system, Indian medicine systems Unani, Siddha and Ayurveda and Amazonian medicine system since plants and herbs are found in nature, remedies derived from them must be safe (Ahemed et al., 2005). There is a growing significance in traditional health systems in providing health care for a wider population in the developing countries (Wilson et al., 2007). Various ethnomedicines rely on herbs for treatment. Herbal medicines are the root of various traditional medicine systems around the world.

Different cultures have developed knowledge about herbal remedies that has been passed from generation to generation constituting what is called traditional medicine (Fakim, 2006). According to WHO, traditional medicine (TM) is defined as diverse health practices, approaches, knowledge and beliefs incorporating plant, animal and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being as well as to threat, diagnose or prevent illness (WHO, 2002). Around 80% of the world’s population lives in developing countries and about 80% of these people use TM systems for their primary healthcare due to affordability and accessibility of the natural sources. On the contrary, developed countries are increasing their use of traditional medicinal plants in the form of rational phytotherapy, dietetics and complementary or alternative medicine. Herbal medicines have been described in traditional texts and used as antimicrobial, anti-inflammatory and antiviral medicines for the cure of allergies, RA infections, wound healing and fever (Borchers, 2000). The development of new anti arthritic drugs is aimed towards the
discovery of safe, potent drugs with minimal side effects (Amresh et al., 2007; O’dell et al., 1998; Badger et al., 1997; Kingsley et al., 1996; Arend et al., 1990).

Natural products offer chemical diversity, structural complexity and a range of biological activities that is not comparable to synthetic approaches. Natural compounds can be used as templates to obtain new chemical entities of pharmaceutical interest. Botanicals provide 25% of currently used crude drugs and around 25% derived from chemically altered natural products (Huxtable, 1992). Nature has been the source of medicinal agents for thousands of years and a notable number of modern drugs have been isolated from natural sources based on their traditional use. Several plant-derived drugs have been developed on the basis of ethno medical information as for example, Reminyl® is a drug developed for the treatment of Alzheimer´s disease derived from galantamine isolated from the genus Galanthus and relatives of the Amaryllis family (Heinrich and Lee, 2004).

Drugs from natural origin have also helped to discover human physiological pathways. For example, Cannabinoids from Cannabis sativa (the hemp plant) lead to the revelation of the endogen cannabinoid system or salicylic acid from Salix alba (White willow bark) lead to the discovery of COX enzymes related to inflammation (Bosch and Banos, 1998). Digoxin from foxglove (Digitalis purpurea L., Scrophulariaceae) lead to the finding of the sodium-potassium ATP-ase pump biochemistry and enabled a better understanding of cardiac pathologies (Rishton, 2008). Muscimol from Amanita muscaria (fly agaric mushroom) has been crucial in differentiating the pharmacology of γ-amino butyric acid (GABA_A and GABA_B) receptor subtypes related to a range of central nervous system disorders.

Several recent surveys reported that there is a significant increase in the discovery of novel active compounds when using ethno pharmacology as a basis for selecting
species for screening compared with random collection of samples (Evans, 2008) so that activity of various plants can be assessed by which the therapeutic values can be expanded (Bani et al., 2007). India has been identified as one of the top twelve mega biodiversity centre of the world. India with its biggest repository of medicinal plants in the world may maintain an important position in the production of raw materials either directly for crude drugs or as the bioactive compounds in the formulation of pharmaceuticals and cosmetics etc. The Indian subcontinent is a vast repository of medicinal plants of around 15000 (Dev, 1997) whereas traditional communities are using only 7,000 - 7,500 plants for curing different diseases (Perumal and Ignacimuthu, 1998; 2000; Kamboj, 2000; Pieroni, 2000). According to another estimate, 17,000 species of medicinal plants have been recorded out of which nearly 3,000 species are used in medicinal field (Nayar, 1987). Because of repeated droughts and scarcity of water the area covered under forests is dwindling gradually. Hence, deforestation and threat of extinction is alarming. Hence, it is the duty of each researcher to provide momentum to step up studies of ethno medicine along with biomedical and chemical terms for the development of novel natural products and drugs for human use.