ABSTRACT
Early inflammatory arthritis can be self-limited disease, develop into rheumatoid arthritis or differentiate into another form of chronic arthritis. The current treatment of rheumatoid arthritis is based on the use of synthetic chemical compounds and natural plants which are having different mechanisms of action known or unknown. Many studies indicate that after or during infection elsewhere in the body, the pathogenetic effective in rheumatoid arthritis are better known today than ever before. This review article is summarized with pathophysiology and their treatments with latest technology, Genomic Association Studies which help to find out the cause of rheumatoid arthritis in less time.

KEY WORDS: Rheumatic Arthritis, Mediators, treatments, Genomic Association Study.

INTRODUCTION
Traditional Pain is very common worldwide in every part of human system. According to the International Association for the study of pain, pain is described as “unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Sowerbutts et al., 2009). Pain is surely the most common reason people seek medical attention and this is particularly evident in the field of rheumatology. The first known clues of arthritis date as far back as 4500 BC. In 1859 the diseases got its current name called rheumatoid arthritis. Pain is the first symptom in the majority of rheumatic disorders (Montecucco et al., 2009). Rheumatoid arthritis has a 19th century pedigree and a 20th century roots. Classification criteria were only developed 50 years ago (Scott et al., 2010). It is a disease of joints causes the pain, swelling, inflammation and deformities. The term “arthritis” covers more than 100 diseases and conditions affecting joints, the surrounding tissues, and other connective tissues (Newell et al., 2005). The cartilage between two the bones damages due to which both bones rub on each other and causes the pain and inflammation. The bones of joints are enclosed in capsule containing fluid which provides lubrication to joints different bones are separated by cartilage in arthritis this cartilage can be damaged. It is a synovial related disease. Two type of pain present in arthritis being acute and chronic related to different causes. Crystal induced arthritis and osteoporotic fractures are the typical examples of acute pain and rheumatoid arthritis and other inflammatory arthritis include osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, juvenile rheumatoid arthritis, gout, bursitis, rheumatic fever, Lyme arthritis, carpal tunnel disease and other disorders (Arthritis Foundation, 1999) are the examples of chronic pain. Pains in rheumatic arthritis are very serious problem in the patients worldwide. Complementary and alternative therapies are available for treatment for arthritis. The therapy of rheumatoid arthritis has been revolutionized by advances in the understanding of disease at a cellular and molecular level accompanied by the technology to target specific mediators of disease. With this paper we would like to focus on the detail study of rheumatic arthritis which will help for the research graduates for understanding the latest lacunae about this topic.

<table>
<thead>
<tr>
<th>Three major types of arthritis in human pathogenesis</th>
<th>Rheumatoid arthritis</th>
<th>Osteoarthritis</th>
<th>Gout</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is auto-immune disorder in which human immune system attacks on their own body</td>
<td>It is condition of wear and tear of cartilage or joints bones rub on each other after cartilage damage. It is degenerative joint disease, pain is due to creating. Burning sensation in muscles and tendons (McAlindon et al., 2007). Due to heavy exercise. May be due the genetic factors.</td>
<td>It is condition of accumulation of uric acid crystal and causes the joint hot, redness, pain and swelling. It is also called metabolic arthritis. About 12% of gout patient are affected due to the diets (Schumacher et al., 2008) taken e.g. - due to alcohol, meat and sugar etc.</td>
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Rheumatic arthritis
Rheumatic arthritis (RA) is chronic and progressive inflammatory disorder. It is chronic poly arthritis with unknown and multifactorial etiology and autoimmune condition that causes synovial cell proliferation, fibrosis, pannus alteration and cartilage and bone erosion leads to pain, stiffness, and swelling of joints which cause the loss of function of joint (American College., 1996). The main symptom of rheumatoid arthritis is inflammation of the synovial membrane (Synovitis)
with pain, heat, swelling, redness and loss of function. If left untreated, synovial fluid will increase, leading to raised pressure in the joint, creating pain and tenderness.

Most affected area is wrist about 75% of RA patients showed wrist symptoms (Sung-Jae Kim et al., 2007, Flatt et al., 1995). This process is regulated by a network of cytokines, prostanoids and proteolytic enzymes which depends upon each other. Pro-inflammatory cytokines such as interleukin-1 (IL-1) (Lubbertset et al., 2005) and tumor necrosis factor-alpha (TNF-α) are central mediators in RA. The concentration of chromogranin A (CgA) and TNF-α are correlated with each other (Comite et al., 2006). Also due to genetic factors (Jorg et al., 2009) but with involvement of environmental factors (Turesson et al., 2006). Mainly two type of receptor are involved Toll-like receptors (TLRs) and NOD-like receptors (NLRs) (William et al., 2009, Neil et al., 2008). Disease related to synovial which causes the cartilage damage (Fedewa et al., 1998, Andreas et al., 2008). In RA the immune system attacks the tissues. RA can affect other organs also like lungs, heart and blood vessels (Gaffo et al., 2006). RA may damage bone and cartilage within the joints, weaken muscles And tendons that support the joints and which ultimately lead to joint destruction (Heijde et al., 1995). RA begins in middle age and occurs more frequently in women than in men. It can affect any joint in the body, but it most often affects the wrist and fingers. It is mostly occurs alternatively in body for example if one hand is affected other will be affected. Culture of RA produces IL-17 it is 17 kDa proteins (Lubberts et al., 2005). In RA loss of regulation of T cell growth and activation. Patient having RA have the more risk of myocardial infarction (Giles et al., 2005, Gonzalez et al., 2005). The disease modifying anti-rheumatic drug’s (DMARD) therapy is used for RA (Machold et al., 2006). A new treatment Immunoablative therapy and hematopoietic stem cell transplantation (HSCT) (Hügle1 et al., 2008). Complementary and alternative medicine (CAM) therapies.

**Diagnosis Criteria**

Early classifications were designed to distinguish established rheumatoid arthritis from other types of established joint diseases. The American College of Rheumatology (ACR) 1987 criteria is limited by poor sensitivity and specificity for classification of patients with early inflammatory arthritis as having rheumatoid arthritis. New criteria has been developed (2007) under ACR called Early arthritis prediction. In the presence of inflammatory arthritis, evidence of systematic inflammation shown by high acute phase reactants and prolonged morning stiffness and auto antibodies in serum based on this, the ACR and European League Against Rheumatism (EULAR) have devised new classification criteria for early arthritis as shown in table 1 (Scott et al., 2010).

**Table 1: Classification criteria of Rheumatic Arthritis according to symptoms**

<table>
<thead>
<tr>
<th>The American College of Rheumatology 1987 revised criteria for rheumatoid arthritis (Arnett et al., 1988)</th>
<th>Arthritic prediction 2007</th>
<th>American college of rheumatology 2010 criteria (Aletaha et al., 2010).</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Morning stiffness of at least 1 hour before maximal improvement</td>
<td>1. Age(multiply by 0.02)</td>
<td>1. Joint involved (0-5)</td>
</tr>
<tr>
<td>2. Arthritis of three joint areas or more</td>
<td>2. Sex(female1)</td>
<td>• One medium-to-large joint(0)</td>
</tr>
<tr>
<td>3. Arthritis of hand joints</td>
<td>3. Duration of involved joints</td>
<td>• Two to ten medium to large joints(1)</td>
</tr>
<tr>
<td>4. Symmetric arthritis</td>
<td>• Small joint hand and feet (0.5)</td>
<td>• Four to ten small joints (large joints not counted)(3)</td>
</tr>
<tr>
<td>5. Rheumatoid nodules</td>
<td>• Symmetrical (0.5)</td>
<td>• More than ten joint(at least one small joint)(5)</td>
</tr>
<tr>
<td>6. Rheumatoid factor positivity</td>
<td>• Upper limbs (1) or upper and lower limbs (1.5)</td>
<td>2. Serology(0-3)</td>
</tr>
<tr>
<td>7. Radiographic changes on hand and wrist radiographs (erosions or decalcification)</td>
<td>4. Morning stiffness (visual analogue scale)</td>
<td>• Negative RF and negative Anti-citrullinated protein/peptide antibodies (ACPA)(0)</td>
</tr>
<tr>
<td></td>
<td>• 26-90 mm(1)</td>
<td>• Low positive RF or low positive ACPA(2)</td>
</tr>
<tr>
<td></td>
<td>• &gt;90 mm(2)</td>
<td>• High positive RF or high positive ACPA(3)</td>
</tr>
<tr>
<td></td>
<td>5. Number of tender joints</td>
<td>3. Acute –phase reaction(0-1)</td>
</tr>
<tr>
<td></td>
<td>• Four to ten(0.5)</td>
<td>• Normal C-reactive protein (CRP) and normal ESR(0)</td>
</tr>
<tr>
<td></td>
<td>• 11 or more(1)</td>
<td>• Abnormal CRP or abnormal Erythrocyte sedimentation rate (ESR)(1)</td>
</tr>
<tr>
<td></td>
<td>6. Number of swollen joints</td>
<td>4. Duration of symptoms(0-1)</td>
</tr>
<tr>
<td></td>
<td>• Four to ten(0.5)</td>
<td>• Less than 6 week(0)</td>
</tr>
<tr>
<td></td>
<td>• 11 or more(1)</td>
<td>• 6 week or more(1)</td>
</tr>
<tr>
<td></td>
<td>7. C-reactive protein (mg/l)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Five to 50(0.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 51 or more(1.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8. RF positive (1)</td>
<td></td>
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<tr>
<td></td>
<td>9. ACPA positive(2)</td>
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</table>
Epidemiology
RA prevalence ranges from 0.33% to 1% in different countries (Marco et al., 1998, Christian et al., 2009). Its incidence is worldwide inhomogeneous, varying among 20 and 50 cases per 100,000 inhabitants in North American and Northern European countries. About 42 million Americans have some form of arthritis. It can affect people of all ages and races. People the prevalence of RA are estimated to be 0.5-1.0% worldwide (Lundkvist et al., 2009). It was estimated 27% of the population of USA suffers from physician diagnosed arthritis and India is one of the country which has been reported sharp increase in the number of elderly persons between 1992 and 2001. The diseases are three times more frequent in women than men. Suggesting hormonal factors have a pathogenic role (Scott et al., 2010).
In the US, the RA affects 2.5 times more in women compared to men. In 2050, the number of elderly persons would rise to about 324 million and 7.7% population related to more than 60 years. Various epidemiological studies in India have shown that musculoskeletal problems are out-numbered. Over two thirds of people with arthritis are younger than 65 years of age (CDC Targeting Arthritis, 2005). Throughout the world, ethnic groups like North America Pima Indians and southeast Alaskan Indians have much higher incidence of RA.

Causes of arthritis
Mainly it depends upon two type factors Genetic Factors and Environmental Factors but other factors are also involved in it.

Genetic Factors
The results of several studies have shown a higher disease concordance among monozygotic twins (12-15%) than dizygotic twins (4%), implying the influence of genetic factors. The data from the past few years have indicated that the HLA DRB1 alleles shared epitope and PTPN22 risk alleles are associated only with a subset of rheumatoid arthritis by presence of ACPA or rheumatoid factor or both (Kochi et al., 2009). Finding of the studies shown that the MHC region harbors the most important genetic risk factors for the ACPA positive disease with PTPN22 as the second most important gene. Several additional risk alleles for the disease have been identified in gene region containing TNF-associated signaling pathway (TRAF1), signal transducer and activation of transcription factor-4 (STAT4) and OLIG3-AIP3 genes. Many genetic study shows that there are very much similarities in two or more arthritic patient in their genetic structure which shows that genetic factor are involved in arthritis. HLA-DRB1 is a special type of allele subtypes (Stastny et al., 1976, Gibofsky et al., 1978) are found in most Yakima and Pima Indians, who have the highest, reported prevalence of RA in the world. The different alleles showed the association study in arthritis (Table 2.)

Table 2: Arthritis susceptible alleles and their mechanism and their genes

<table>
<thead>
<tr>
<th>Disease susceptibility alleles</th>
<th>Gene product</th>
<th>Suggested mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DRB1–shared epitope alleles</td>
<td>HLA-DRβ chain</td>
<td>T-cell selection and maturation</td>
</tr>
<tr>
<td>TNFSR11A</td>
<td>RANK (receptor activator of nuclear factor)</td>
<td>Osteoclast differentiation</td>
</tr>
<tr>
<td>CRHA2</td>
<td>CRH (corticotropin-releasing hormone)</td>
<td>Defective HPA response to inflammation</td>
</tr>
<tr>
<td>Slc2F2T</td>
<td>SLC22A4 organic action transporter</td>
<td>Regulates lymphocyte activation in secondary lymphoid organs and/or contributes to local inflammation</td>
</tr>
<tr>
<td>Runx1</td>
<td>RUNX1 (Runt-related transcription factor)</td>
<td>Regulates expression of SCL22A4</td>
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</tbody>
</table>

Environmental factors
There are various environmental factors (Figure 2) due to which arthritis takes place. Like life style factors e.g. smoking, diet (Deborah et al., 2001), RA in smokers causes more problems than non-smokers problems may be like nodules (Masdottir et al., 2000), Harrison et al., 2001. Smoking is associated with RF and ACPA production. In addition, smoking multiplies the adverse effect of the HLA-DRB1 shared-epitope alleles. Several causes the infections microorganisms also initiate the intermediate related to RA. Diet fish oil, olive oil has the protective action in RA. Omega 3 fatty acids contents are also protective action in RA. The best environmental factors associated with arthritis is smoking seems to be positive relation with HLA-DRB1 shared-epitope alleles other factors include fish oil, saw dust and silica gel.

Other factors
Age and sex are also important factor to identify the cause and prevalence of arthritis. The RA ratio was reported on age basis in female and male was 3:1 (Tobón et al., 2010). With increasing age the chances of arthritis increases (Eberhardt et al., 1990, Pease et al., 1999). Most sensitive age for arthritis is 20-30 but its symptoms appear mostly after 35 or 40. Sex hormones are the other factor in the immune response, with estrogens as enhancers.
at least of the humoral immunity and androgens and progesterone as natural immune-suppressors In female’s, estrogen stimulate the immune system and in males, low level of testosterone was observed (Barrett et al., 1999), bacteria, virus, Epstein-Barr virus, parvovirus B-19, rubella and retrovirus may infect an individual with the appropriate genetic background through some mechanism, the inflammatory response becomes focused on self antigens.

Pathophysiology
Rheumatoid arthritis is called a complex genetic disease, meaning that several genes, environmental factors, and stochastic factors act in concert to cause pathological events. Findings of twin studies have estimated the relative contribution of genetic factors to be about 50% for the entire syndrome of rheumatoid arthritis, leaving the remaining part to environment and chance (Scott et al., 2010). The role of the mediators of inflammation, cytokines, growth factors, chemokines, adhesion molecules and matrix metalloproteinase has not been clearly defined in the pathogenesis of RA. These substances appear to be involved in attracting, proliferation and phenotypic transformation of synoviocytes into pannus. Pannus behaves similar to a locally invasive tumor by invading and eroding articular cartilage, subchondral bone, tendons and ligaments.

1. Inflammation through receptor
2. Inflammation through intermediates mediators

Inflammation through receptors
Some of receptors called Pattern recognition receptors (PRRs) implicated in various inflammatory arthropathies which leads to activation of cytokines (figure 1). These receptor also sense microbes (William et al., 2009). Microbial molecules are found in joint of RA patient which activates inflammatory reactions (Heijden et al., 2000).

1. Toll-like Receptors (TLRs)
2. NOD-like Receptors (NLRs)

Toll-like receptor
There are ten TLRs are known in human but the function of nine is known (TLR1 to TLR9). e.g. TLR2 senses lipopeptides from bacteria. TLRs10 is not determined (Neill et al., 2008). The signaling pathway of TLR’s involves adapter proteins Myeloid differentiation primary response gene (88)(MyD88), Nuclear factor-kB (NFkB) which makes some nucleic acid change leads to release of pro-inflammatory cytokines (Kenny et al. 2008). TLRs antagonist having a very improving effect in RA disease its study had been conducted on Rats (Joosten et al., 2007).

Figure 2: Picture of factors affecting arthritis (Klareskog et al., 2009)
NOD-like receptors
These are intracellular receptors. This family consists of 22 cytoplasmic proteins including the Nucleotide-binding oligomerization domain-containing protein (NOD) or NALP. One nucleotide binding domain and other is leucine rich C-terminus (William et al., 2009). Using NOD1 and NOD2 knockout mice, Joosten and colleagues have shown a pro-inflammatory role for NOD2 and an anti-inflammatory role for NOD1 in a streptococcal cell wall induced model of arthritis (William et al., 2009).

Inflammation through intermediates mediators
- **Cluster of differentiation (CD4+CD25+T) cells**
  In human glycoprotein CD4+CD25+ Tregs increases in peripheral circulation in RA. The CD4+CD25+ T cells might function as potential regulators of immune responses in RA (Wahl et al., 2005). CD4+CD25- T cell prevent experimental induced RA (McHugh et al., 2002, Mottet et al., 2003). First one is that the CD4 + CD25+ T cell expresses chemokine receptor in RA. CXCR4, CCR4 are highly expressed in synovial. CD4 T cells are also in healthy human but the active retention in RA. Second is the accumulation of CD4+CD25+ T cells in synovial related to IL-2 because the synovial fluid contains high levels of inflammatory cytokines. Third is that inhibition of T-cell to undergo apoptosis due to which the T-cell in synovial increases. Function of CD4+CD25+Tcells in synovial: Synovial CD4+CD25+ T cells display an even increased suppressive capacity compared with blood CD4+CD25+ T cells in RA.
- **Interleukin-17 (IL-17)**
  It is 17 kDa protein cell cytokine spontaneously produced by cultures of rheumatoid arthritis (RA) synovial membranes. IL-17 is a pro-inflammatory cytokine produced only by cells of the immune system (Chen et al., 2000, Shi et al., 2000), which is consider as activator in RA. The concentration of IL-17 is more in RA than osteoarthritis (Ziolkowska et al., 2000, Chabaud et al., 1999). It is a stimulator of osteoclastogenesis which promote the collagen degradation in synovial. This ultimately causes the bone destruction (Lubberts et al., 2001).
- **Tumor necrosis factor-α (TNF-α)**
  TNF has an important role in pathology of RA. Some evidence shows that RA is a systemic disease. CgA is correlated with the TNF-α during disease the concentration of CgA is higher in blood more than the synovial (Capellino et al., 2008). TNF-α is used as a target for the treatment RA by using its antagonist (Maini et al., 2000, Taylor et al., 2001).
- **Chemokines**
  Chemokines are small chemo attractant proteins that have a prominent role in leukocyte recruitment and activation in sites of inflammation. They are ligands for G-protein-coupled receptors on the surface of leucocytes. The distribution of chemokine and receptor expression is variable, which means that specific leukocyte subsets can be recruited. Numerous chemokines are thought to be active in the synovium of patients with rheumatoid arthritis, but their function with regard to leukocyte subset recruitment and activation is unknown.
- **Matrix metalloproteinase**
  Metalloproteinase are produced at high levels by type B synoviocytes in rheumatoid arthritis. Metalloproteinases are a family of enzymes required for remodeling and destruction of extracellular matrix. The activity of the matrix
metalloproteinases is regulated by molecules such as tissue inhibitors of metalloproteinases (TIMPs), serine proteinase inhibitors (SERPINS) and macroglobulin. In rheumatoid arthritis, high levels of metalloproteinase activity are thought to contribute to cartilage and bone degradation (McCachren et al., 1990, Gravallese et al., 1991).

- **Adhesion molecules**

Adhesion molecules are thought to have a role in recruitment of inflammatory cells to the joints in rheumatoid arthritis. The presence of adhesion molecules, which confer cells with the ability to adhere to each other and the extracellular matrix, is the central to various biological processes including homeostasis, vascular and epithelial integrity, immune responses, and organogenesis. Analysis of rheumatoid arthritis synovial tissue indicates that many families of adhesion molecules are expressed in patterns appropriate for modulating cell retention in the rheumatoid arthritis synovium (Hale et al., 1989, Johnson et al., 1993).

- **Angiogenesis**

Angiogenesis—the process of new blood-vessel formation—is highly active in rheumatoid arthritis, particularly early onset disease (FitzGerald et al., 1991). The newly formed vessels provide oxygen and nutrients to the hypertrophic synovium, and provide the means for recruitment of inflammatory cells to the joint anatomical compartment. Generally, angiogenesis is tightly regulated by many inducers and inhibitors. In the basal state, vascular endothelium is quiescent and fewer than 0.01% of endothelial cells divide (Koch et al., 1998). In physiological processes such as wound repair or the female reproductive cycle, and pathological processes such as tumor growth and rheumatoid arthritis, this quiescent tissue can be rapidly stimulated to proliferate. A growing list of angiogenic factors including cytokines, growth factors, colony stimulating factors, and soluble adhesion molecules has been described in the synovium and synovial fluid of patients with rheumatoid arthritis (Koch et al., 1998).

**NEW INTERMEDIATES INVOLVED IN ARTHRITIS**

- **Sphingosine-1-Phosphate (S1P)**

Sphingosine-1-phosphate (S1P) is a signaling sphingolipid and a bioactive lipid mediator. It is well recognized as a regulator of angiogenesis, vascular homeostasis and permeability (Alvarez et al., 2007), the most recent evidence indicated that S1P was a critical regulator of T-cell and B-cell trafficking (Melendez et al., 2008) and macrophage function (Weigert et al., 2009). Thus, the binding of S1P to its receptors, S1PR1/S1PR2, triggers and is required for stimulating the movement of immune cells from the thymus and lymph nodes into lymphatic vessels from where they can travel through peripheral circulation to synovial joints. Additionally, it was shown that the secreted form of S1P also regulated cell survival and apoptosis by its capacity to bind to and activate specific G protein-coupled receptors, S1P1-S1P15 (Hait et al., 2006).

- **IL-7 Receptor**

Expression of the IL-7 receptor (IL-7R) gene (also known as CD127) plays a central role in thymocyte development (Saini et al., 2009), T-cell survival, B-cell maturation, T-cell-dendritic cell (DC) interactions (Vogt et al., 2009) as an inducer of lymphoid tissue development (Schmutz et al., 2009) as well as being useful for identifying Tregulatory (Treg) cells producing the FoxP3 phenotype (Banham et al., 2006). To function normally, the IL-7R requires the presence of the IL-2 receptor gamma chain (IL-2Rγ) which is the common γ-chain that is shared by the receptors of various cytokines including IL-2, -4, -7, -9, -15 and -21. IL-7R was also found to important in regulating the accessibility of the T-cell receptor (TCR) γ locus (TCR-γ) by STAT5 and histone acetylase (Malemud et al., 2008). Thus, over expression of IL-7Rα is likely to be highly relevant to the pathogenesis and even to the progression of inflammatory arthritis.

- **Spleen Tyrosine Kinase**

Spleen tyrosine kinase (SyK) and ζ-chain associated protein-70 (ZAP-70) are non-receptor kinases that are primarily expressed in hemopoietic cells, including cells of the spleen, mast cells, neutrophils and macrophages. Syk and ZAP-70 are also involved in T-cell and B-cell receptor signaling potentially making Syk and ZAP-70 enzyme targets for the treatment of autoimmune diseases (Wong et al., 2004). The reduced expression of Syk in the R788-treated mice correlated with an amelioration of clinical arthritis, a reduction in pro-inflammatory chemokines and cytokines, including the CXCR2 ligand KC-GRO-α, macrophage chemo attractant protein-1 (MCP-1), IL-1, and IL-6, as well as inducing suppression of cartilage oligomeric matrix protein release, the latter protein a sensitive in vitro biomarker for articular cartilage extracellular matrix degradation.

- **MEK/ERK 1/2**

ERK 1/2 belongs to the SAP/MAPK family of protein kinases. This must be activated before it can act as a fully activated protein kinase and the activation of an MAPK such as ERK 1/2 is generally carried out by one of at least 7 upstream
MKK proteins (Malemud et al., 2004). Moreover, MKK activity is also regulated by further upstream MKKK and MKKKK activity that are either tyrosine or serine-binding proteins which may also require low molecular weight GTP-binding proteins for MKKK activation. MEK is the key regulatory protein kinase activation in the Ras/Raf/MEK/ERK pathway. In that regard, MEK is critical for the up regulation of several pro-inflammatory cytokines, including, TNF-α, IL-1β and IL-6. (Breitkreutz et al., 2007).

• Mitogen-Activated Protein Kinase 5/p38 Kinase Regulated/Activated Protein Kinase
 Mitogen-activated protein kinase 5 (MK5) also known as p38 kinase regulated/activated protein kinase (PRAK) is a 471 amino acid protein with a 20%-30% sequence identity to the cyclic AMP responsive element binding protein, CREB-phosphorylating MAPK-regulated protein kinase RSK-1, -2 and -3 (New et al., 1998). MK5/PRAK was found to be expressed in most human tissues and activated by cell stressors and pro-inflammatory cytokines in vitro. In turn, PRAK activity was regulated by p38α and p38β activity. Once activated, MK5/PRAK was reported to directly phosphorylate heat shock protein 27 (Hsp27), the latter having been implicated in several physiologically relevant immune-mediated inflammatory responses such as CD8+ lymphocyte subset expansion and apoptosis resistance as well as in the activation of the Toll-like receptor-4 in monocytes-derived RA DCs (Roelofs et al., 2006).

• Micro RNAs
Micro- RNAs (miRs) are small non-coding RNA molecules composed of double-stranded RNAs of 21–25 nucleotides derived from endogenously expressed transcripts with characteristic hairpin structures. miRs are known to negatively regulate gene expression at the posttranscriptional level.

• Inhibition of Proteasome Activity
Proteasomes are large protein complexes that reside in both the nucleus and cytoplasm of eukaryotic cells (Peters et al., 1994). A principal function of the 26S-proteasome is to regulate the concentration of completed proteins within a cell as well as to participate in the controlled degradation of mis-folded proteins that is independent of enzyme activity within lysosomes. The figure 3 shows the different mediators involved in arthritis.

Various techniques for diagnosis of arthritis
• Rheumatoid factor
It is the mainly used laboratory method used for the determination. The rheumatoid factors (RF) are antibodies directed against the fragment crystallizable region (Fc) portion of the Immunoglobulin G (IgG) immunoglobulin’s and are found in 75–80% of patients affected by RA (Tampoia et al., 2005). For which the result has been positive in < 5% of normal control subjects. It is detected by enzyme-linked immunosorbent assays (ELISAs) for quantitative detection of RF isotypes IgG, IgA and IgM (Visser et al., 2002). IgM RF discriminates well between RA and non-RA conditions (Wolfe et al., 1991).

• The filagrin–citrulline protein system
First Nienhuis and Mandema described the anti-perinuclear factor (APF) discovered by Nienhuis and Mandema (Nienhuis et al., 1964). This test is very less use in laboratories although, it is specific for RA. APF are reported to be present in 40–90% of patients with established RA. Determination of protein (pro) filaggrin in buccal mucosa cells by means of the indirect immunofluorescence test (IIF). It is confirmed and extended by the biochemical characterization of (pro) filaggrin as the antigen in both the APF test and the related so-called anti-keratin antibody (AKA) test. The APF/AKA antibodies are therefore, more correctly referred to as ‘anti-filaggrin’ antibodies (Sebbag et al., 1995, Schellekens et al., 1998).

Figure 3:- Pathophysiology of Arthritis involving various mediators
• Conventional X-rays
It is imaging technique used for the diagnosis of RA. It shows the deformities in joints on a X-ray (figure 4).
Early erosion in foot or hand can be detected by conventional X-ray method. In the Leiden early arthritis clinic, 15% of the 524 early arthritis patients had erosions on X-rays of hands or feet at the first visit (Visser et al., 2005).

- **Ultrasound and magnetic resonance imaging**
  It is more effective than the conventional X-rays method detect more erosion (Ostergaard et al., 2003). It less used due to its high cost and more examination time. Another disadvantage of ultrasound is dependency on skills of operator. It is more sensitive tool of assessing inflammation than physical examination (Tampoia et al., 2005).

- **Detection of Presence of autoantibody**
  A) Anti-SA antibodies (Despres et al., 1994).
  B) Anti-RA33 antibodies (Hassfeld et al., 1993).
  C) Anti-p68 nucleoporin 68 (BiP) antibodies (Blass et al., 2001).
  D) Autoantibody profiling: proteomics (Tampoia et al., 2005).

- **Erythrocyte sedimentation rate**
  Erythrocyte sedimentation rate (ESR) determination is one of the method tells about the settlement of red blood cells rate in ESR tube which is used for the Arthritis (Green et al., 2002).

- **Cytokine determination**
  One more method to assess the arthritis is the determination of the pro-inflammatory cytokines. Several cytokines which function as immunological mediators of inflammation may also cause joint destruction in rheumatoid arthritis (RA). Interleukin 1 stimulates the secretion of prostaglandin E2, platelet derived growth factor, and collagenase by fibroblasts and chondrocytes, and the proliferation of fibroblasts and their production of fibronectin, type I collagen, and proteoglycans (Kahle et al., 1992).

A new way investigation through pharmacogenomics study
Genome wide association studies are the most comprehensive and straight forward approach to teasing out the identity of genetic polymorphisms associated with any given disease or characteristic. The capacity to detect very small differences between disease and control populations and the reporting of such associations clearly demonstrates that the low-hanging fruit of genetic disease associations has been picked and we are now harvesting the fruit from the top of the tree. (HLA)-DR4 gene is less specific for RA encodes a special sequence of amino acid called shared epitope (SE) of the human leukocyte antigen (Kim et al., 2000).

**Prevention before treatment**
- By changing life style.
- By taking healthy diet.
- By doing weight losing exercise (Khurana et al., 2005).
- By Stop smoking for those who smoke (Daniel et al., 2008).

Previously known SNPs associated with rheumatoid arthritis risk in Europeans (Stahl et al., 2010)

<table>
<thead>
<tr>
<th>Locus</th>
<th>ID</th>
<th>SNP Gene(s)</th>
<th>Minor allele</th>
</tr>
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<tbody>
<tr>
<td>1p36</td>
<td>rs3890745*</td>
<td>TNFRSF14</td>
<td>C</td>
</tr>
<tr>
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Duration of anti arthritis Treatment
The total duration of treatment normally 3-12 months this includes prescribed by different combination of anti arthritis drugs as shown in figure 4

![Figure 4: Duration of anti-arthritits treatment](image)

Established treatments
The key aim of treatment for established rheumatoid arthritis is minimization of disease activity. There are different drugs which act on various receptors and mediators to treat inflammation as figure 5.

Another alternative treatment
Immunoadblative therapy and hematopoietic stem cell transplantation (HSCT)
Hematopoietic stem cells (HSCs) are progenitor cells of platelets, erythrocytes, granulocytes, B and T lymphocytes, monocytes, tissue macrophages. Various animal studies show that these cells play an important role in RA. European Group for Blood and Marrow Transplantation/European League against Rheumatism (EBMT/EULAR) working on RA collects the data on 1000 patient which were treated with (HSCT). In this therapy the aggressive immune modulating cells are replaced by non aggressive cells. An effective transfer prevents the symptoms and cures the RA (Tyndall et al., 2002).

Gene Therapy
The first human gene transfer is held in 1989. Rheumatoid arthritis (RA) had become an early target for gene therapy in the early 1990s and beginning clinical trials in 1996. The first International Meeting on the Gene Therapy of
Arthritis and Related Disorders (GTARD) was held at the National Institutes of Health (NIH) (Bethesda, MD, USA) in 1998. In this therapy the gene is transferred in target cell by the help of any viral and non viral vectors (Evans et al., 2009). Oncoretroviruses, such as the moloney murine leukemia virus was first used vector for RA gene transfer, other vectors used are Adenovirus vectors.

**Complementary and alternative Medicines (CAM)**

In India 33% patient are found to be used CAM therapies [71]. CAM therapies are safer and more natural. These may be botanical, dietary (Berman et al., 2004) and other mineral preparations.But these treatments are without preclinical studies hence less faith on these drugs. e.g.: - Fish oil, Valerian, Ginger, Curcumin, Boswellia etc.

**Nutraceutical used as therapeutic agents in Arthritis**

It is interesting to see the increasing use of nutraceutical in the treatment of various diseases because of their presumed safety and potential nutritional and therapeutic effects. Some time it also called functional food. Functional food provides the body with the required amount of vitamins, fats, proteins, carbohydrates necessary for healthy survival but when it is given for the treatment of any disease or prevention of any disease it called as Nutraceutical (Rajasekaran et al., 2008).

**Omega-3 and Omega-6**

The important role in treating the Arthritis by generating potent modulatory molecules for inflammatory responses, including eicosanoids (prostaglandins, and leukotrienes), and cytokines (interleukins) and affecting the gene expression of various bioactive molecules. Gamma linolenic acid (GLA, all cis 6, 9, 12-Octadecatrienoic acid, C18:3, n-6), is produced in the body from linoleic acid (all cis 6, 9-octadecadienoic acid), an essential fatty acid of omega-6 series by the enzyme delta-6-desaturase. Preformed GLA is present in trace amounts in green leafy vegetables, nuts, vegetable oils, such as evening primrose (Oenothera biennis) oil, blackcurrant seed oil, borage oil and hemp seed oil, and from spirulina, cyanobacteria. It is a nutraceutical used for treating problems with inflammation and auto-immune diseases (James et al., 2003).

**Glucosamine**

This naturally occurring substance, found in high concentrations in joint structures, is a rate-limiting step in glycosaminoglycan (GAG) synthesis and joint cartilage repair. Thus, when given as a supplement it is said to stimulate the manufacture of cartilage components and the incorporation of sulphur into cartilage, thereby producing the substances necessary for proper joint function and for stimulating joint repair (as far as this is possible); This therefore addresses the cause rather than suppressing symptoms (Ritchie et al., 2005).

**Chondroitin sulphate**

These are long chain polymers, which are the major GAGs found in cartilage. Oral administration of this as a supplement has been found to have similar results to Glucosamine. It is said to be an effective and direct inhibitor of degradative enzyme activity and long term trials have shown supplementation to slow the progression of Osteoarthritis, to improve joint mobility, reduce pain and radiographic evidence of reversal has been seen. This is often given in combination with Glucosamine (Ritchie et al., 2005).

**MSM (Methylsulfonylmethane)**

MSM is a source of organic sulfur found naturally in the human body and in many foods. Sulfur is well known in maintaining the connective tissue. MSM provides additional elemental sulfur to aid the body in the repair process of these tissues. MSM may support the body in regulating insulin production, improving skin smoothness and elasticity, regulating environmental and allergic sensitivities. Lastly sulfur is a key element necessary in the detoxification processes which is highly valuable in many patients with arthritis (Usha et al., 2004).

**Bromelain**

Bromelain is a proteolytic enzyme complex derived from the stalk of the pineapple plant which demonstrates anti-edematous, anti-inflammatory, anti-thrombotic and fibrinolytic activities. Bromelain’s therapeutic actions are only partially due to its enzymatic activity and were able to induce increased natural killer cell activity in immunocompromised individuals. Studies comparing bromelain’s anti-inflammatory effects against pharmaceuticals demonstrate greater levels of improvement and decreased dependency on analgesics (Usha et al., 2004, Cohen et al., 1964).

**GLA**

The most significant source of GLA for infants is breast milk. GLA is further metabolized to dihomo-gamma linlenic acid (DGLA) which undergoes oxidative metabolism by cyclooxygenases and lipoxygenases to produce anti-inflammatory eicosanoids.

**Elements and miscellaneous**

**Selenium:** This is an antioxidant that may be deficient in rheumatoid arthritis patients (Rotruck et al., 1973).
**Vitamin E:** Vitamin E is a antioxidant that works with selenium.

**Zinc:** Zinc is a powerful antioxidant and is generally deficient in those suffering from rheumatoid arthritis.

**Vitamin C:** This is an antioxidant and many who suffer from rheumatoid arthritis are deficient (Zhong Fang et al., 2002).

**Pantothenic acid:** A deficiency may cause a failure in the growth of cartilage produce arthritis like symptoms.

**Calcium and Magnesium:** These can help to prevent bone loss.

**Methionine:** This is an essential amino acid that is important to the structure of cartilage and can act as a natural anti-inflammatory.

**Cat’s claw is a rich source of phytochemicals:** 17 alkaloids, along with glycosides, tannins, flavonoids, sterol fractions, and other compounds (Zhang et al., 2005).

**Herbal plants extract treatment**

Various well established pre-clinical models of arthritis which are used to studying the effect of anti-arthritic activity of herbal extracts.

**Collagen type II induced hyperimmunised arthritis in rats**

It is widely used method to induce the arthritis in animal models. When collagen is introduced, it is immediately captured by antigen presenting cells (APCs). Disease involves activation of both T & B cells that are antigen-specific & auto reactive. T cell & T cell-derived cytokines promote differentiation & activation of macrophages, osteoclasts & fibroblast, leading to arthritis (Doncarli et al., 1997). 2.0 mg/ml collagen is dissolved in 0.1 M acetic acid and placed at 4 °C overnight. This solution is added to chilled and 0.5 ml of incomplete Freund’s adjuvant drop wise. 1 ml of the above solution is given to the rats on the five different sites which contains the 0.5ml of collagen and 0.5 ml of incomplete Freund’s adjuvant in equal amount. Control animals receive only incomplete Freund’s adjuvant in 0.1 ml acetic acid.

On 20th day the hind limbs measured plethysmographically. The animals with paw volume of 1.8 ml or more are used for further testing. 20-40 days animal receive the test drug on day 41 the paw volume is measured again and compared with the above (Doncarli et al., 1997).

**Complete Freund’s adjuvant induce arthritis in rat**

It is the best and most widely used method for the arthritis produces the symptoms of arthritis. It is sensitive for both immune system inhibiting and anti-inflammatory activity. On day zero rats are injected on the sub planter region on left hind paw with 0.1 ml of complete freunds adjuvant. This consists of 6mg Mycobacterium butyricum suspended in heavy paraffin oil at a dose of 6 mg/ml. Both standard and test are administered on the same day and dose is given for 12 days (Kannan et al., 2005).

**Streptococcal cell wall method for Arthritis:** - The streptococcal cell wall model of arthritis in female Lewis rats is one of the most reliable and best characterized experimental models of RA. Schwab and colleagues described SCW arthritis in the 1970. A single injection of streptococcal can produce severe and erosive arthritis. As in human RA, female rats develop arthritis more readily than male rats which show the factor that female human is more susceptible to arthritis (Kannan et al., 2005). The high female susceptibility is due to high estrogen level in the blood.

**Cartilage oligomeric matrix protein (COMP) induced arthritis**

Immunization with COMP in IFA induces severe arthritis in susceptible rat strains, such as DA and LEW. Although the peripheral joint arthritis clinically resembles RA, COMP-induced arthritis, however, does not result in the permanent destruction of joints. Disease development appears to be dependent on an immune response to autologous COMP and not on cross-reactivity to other cartilage rat collagens (Newbould et al., 1963, Di Rosa et al., 1972).

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**Mechanisms of immunomodulation by herbal products**

(Shivaparasad et al.2010)

<table>
<thead>
<tr>
<th>Mechanisms of immunomodulation by herbal products</th>
<th>Cellular and humoral responses</th>
<th>Cytokine response/balance</th>
<th>Cellular migration into the target organ</th>
<th>Mechanism of action not yet determined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on T cell response (T cell activation, T cell proliferation, ratio of CD4+/CD8+ cells, etc.) e.g. - Pterodon pubescens etc.</td>
<td>Induction/expansion of regulatory T cells e.g. - Chelidonium majus etc.</td>
<td>Change in antibody/B cell response e.g. - Camellia sinensis etc.</td>
<td>Affecting major cytokines produced by macrophages/ antigen-presenting cells (TNF-α, IL-1, IL-6, etc.) and/or deviation of the response to Th2 type e.g. - Swertia chirayita etc.</td>
<td>Inhibiting the pathogenic cytokine IL-17 and related cytokines e.g. - Tripterygium wilfordii etc.</td>
</tr>
</tbody>
</table>
DISCUSSION AND CONCLUSION
With the evolution of industrialization, globalization and economic liberalization with the Technology Up gradation of the individual life of style was changing. People with the type of inheritance are predisposed to certain diseases triggered by factors existing lifestyle. Food, style of life and environment are three important determinants related to the cause of the disease. An inadequate intake of nutrients, consumption junk food and beverages such as tea, coffee, alcohol decreased strength and energy to the defense mechanism of the body. Environmental pollution is the result of industrialization and deforestation, threatening the health of residents. People engaged in long hours night shifts, and physical inactivity has led to sedentary lifestyle. This paper is focused on etiology of arthritis through different pathophysiology, investigation techniques and their allopathic treatments. Already new insights into the various molecular pathways have been used to develop new and very efficient treatment approaches for the patients. Apart from this, natural products can contribute to the suppression of inflammation and artistic processes. Despite making major progress in rheumatoid arthritis research, still genetically this disease is not in control. So, with new investigation tool called pharmacogenomics studies which will help to find out the allele which is responsible for arthritis in different races, population and ethnicity. On the basis of pharmacogenomics studies, we need to find out how the best target these drugs to the right individuals at the right time. Finally it is concluded that with pharmacogenomics study we can treat and minimize the prevalence rate of rheumatoid patients at globally.

CONFLICT OF INTEREST
There are no conflicts of interest

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