



## **A Comprehensive Review on Rheumatoid Arthritis**

**R. S. Nithyashree<sup>1</sup> and R. Deveswaran<sup>1\*</sup>**

<sup>1</sup>Department of Pharmaceutics, Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences,  
MSR Nagar, Bangalore, 560054, India.

### **Authors' contributions**

*This work was carried out in collaboration between both authors. Author RD conceived the idea, checked and revised the manuscript. Author RSN managed the literature searches and wrote the first draft of the manuscript. Both the authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/JPRI/2020/v32i1230556

#### Editor(s):

(1) Dr. Rafik Karaman, Al-Quds University, Palestine.

#### Reviewers:

(1) Ya-Fei Liu, Hospital of Zhengzhou University, China.

(2) Katia Nunes Sá, Brazil.

(3) Jose Fernando Marques Barcellos, Federal University of Amazon, Brazil.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/58826>

**Review Article**

**Received 08 May 2020**

**Accepted 13 July 2020**

**Published 27 July 2020**

### **ABSTRACT**

Rheumatoid arthritis is an enduring inflammatory disease that is categorized by bumping off the joint and rigidity, bone and cartilage devastation all above the joints. It is an autoimmune disease or disease caused by factors like smoking, obesity, etc. Cytokines are the main inducers for rheumatoid arthritis which produce interleukin 1 $\beta$  and interleukin 6 factors that cause the devastation of synovium and cartilage present at the joints. The deformation of skeletal muscles is observed in an arthritic patient. The present review is a discussion on rheumatoid arthritis that includes etiology, pathology and pathogenesis, signs and symptoms, clinical complications, diagnosis, treatment, therapy, certain patents and applications. The patents include the development of numerous novel techniques for the management of rheumatoid arthritis and diseases associated with rheumatoid arthritis. The targets to treat rheumatoid arthritis are interleukins, tumor necrosis factor-alpha, sialoprotein I and several other factors. Different biomarkers are used for different types of rheumatoid arthritis and the mechanism also varies. Certain marketed formulations were enlisted. Recent trends in the management of rheumatoid arthritis are the main concern of this article.

\*Corresponding author: E-mail: [deveswaran.ps.ph@msruas.ac.in](mailto:deveswaran.ps.ph@msruas.ac.in);

Keywords: Rheumatoid arthritis; TNF- $\alpha$ ; IL; inflammation; synovium.

## ABBREVIATIONS

TNF: Tumour Necrosis Factor; IL: Interleukin; SC: Subcutaneous; Ig: Immunoglobulin; NSAIDs: Non-steroidal Anti-inflammatory Drugs; DMARDs: Disease-modifying anti-rheumatic drugs; BVT: Bee Venom Therapy; MMP: Matrix Metalloproteinase.

## 1. INTRODUCTION

Rheumatoid arthritis is an enduring inflammatory disease that is categorized by bumping off the joint and rigidity, bone and cartilage devastation all above the joints. The disease is allied with the molecules of major histocompatibility complex, dependent T- Cells. This disease is more severe in the case of women rather than men and in the elder population [1]. The outcome of the disease is inflammation of the joints systemically, persistent synovitis, damage of the tissues due to the release of cytokines and inflammation due to imbalance between the autoimmune cells. The autoimmune antibodies will damage the tissues

[2]. The occurrence of rheumatoid arthritis is 1% in the adult population. This disease is at 42<sup>nd</sup> place for the main cytology of comprehensive frailty. Rheumatoid arthritis death related to cardiac diseases and complications associated with pulmonary is 10-20% and 60-80% [3]. Currently, patients with rheumatoid arthritis have parallel occurrences associated with an increased risk rate of cancer during therapy or after the therapy [4]. During the 1970s, rheumatoid arthritis was detected by analyzing the synovial fluid of the patients and the elevated intensities of prostaglandins were identified. The different arachidonic acid metabolites were produced from the arachidonic acid pathway

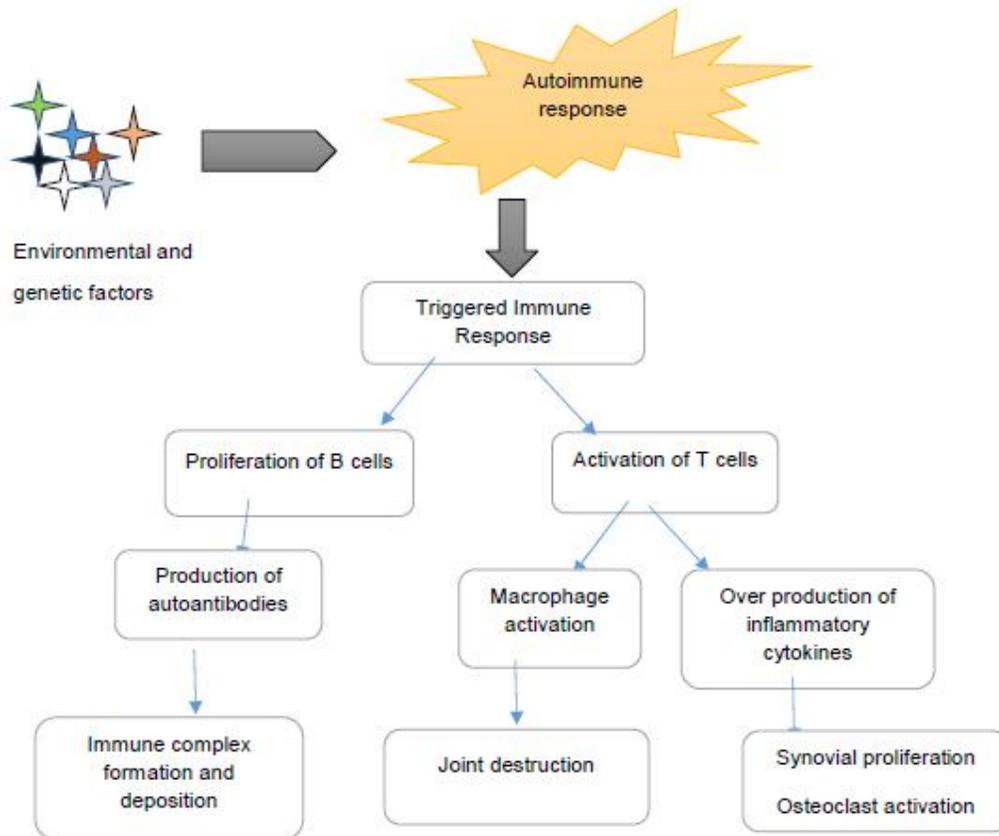


Fig. 1. Stages of rheumatoid arthritis

which is responsible for the depletion of bone and cartilage. As the metabolites of arachidonic acid produce inflamed synovium that results in inhibition of the cell proliferation. The cyclooxygenases produce two types of isoforms namely COX-1 and COX-2 where COX-2 are induced in inflammatory situations and the expressions are more in the tissues of synovial in the patients with rheumatoid arthritis [5]. The drop in the swollen synovitis and clampdown in the devastation of joints is observed with the use of disease-modifying anti-rheumatic drugs like methotrexate [6]. Other drugs used in the treatment of rheumatoid arthritis are dexamethasone (glucocorticoid), lornoxicam (non-steroidal anti-inflammatory drugs) [5]. New choices are made in the treatment of rheumatoid arthritis. The biological molecules with high pharmacological perspicacity and lesser side effects are selected. Stability and economic (expensive) are the major challenges to develop and use biological products. Since synthetic drugs have the highest possibility of adverse events, nowadays, natural/herbal drugs are more prominent. Some of the natural molecules possessing anti-rheumatic activity are brazilin,  $\beta$ -elemene, cardamonin, bufalin, celastrol, curcumin, isogarcinol, etc [7]. The reason for the impairment of joint is due to the multifaceted interaction of the immune modulators. In the progress of rheumatoid arthritis, few cells like B cells, T cells, macrophages (synoviocytes) play a major role in the advancement of immunological actions. B cells will improvise the inflammatory process by producing autoantibodies like rheumatoid factor, anti-citrullinated protein antibody. T cells will activate macrophages which indeed will cause the overproduction of inflammatory cytokines like TNF- $\alpha$ , IL-1 $\beta$ , IL-6. The amplified fabrication of T and B cells will result in the fabrication of cytokines and chemokines leads to the raise in the T cell, B cell, and macrophage interface. Inflammatory cytokines will persuade the cells of synovial to discharge tissue mortifying matrix metalloproteases. Bone erosion occurs due to the progress of osteoclast by TNF- $\alpha$  [8].

## 2. ETIOLOGY

The cause for the occurrence of rheumatoid arthritis is unknown. It might be due to a change in response of a genetically susceptible host to an infectious agent. The causative agents may

include Mycoplasma, cytomegalovirus, Epstein-Barr virus, rubella virus, and parvovirus. The distinctive spreading of an infectious agent that causes chronic inflammatory arthritis is unknown.

The relevant factors influencing rheumatoid arthritis

- a. Genetic and environmental factors
- b. Smoking
- c. Human microbiome

### a. Genetic and environmental factors:

The genetic impact for rheumatoid arthritis is between 30% and 60% from the multiple genetic studies. The most significant genetic factor related to rheumatoid arthritis is "shared epitope" which is present in the DRB1 allele. The three-fold increase in the occurrence of rheumatoid arthritis is in relation to the presence of a shared epitope.

### b. Smoking:

Smoking is the main risk factor for the development of many chronic diseases. According to a few cohorts, the risk for the development of rheumatoid arthritis is more in ACPA-positive individuals who consume coffee. The relative risk factor is 2.06 with people who consume more than four cups of coffee. A Swedish cohort says that work-related exposure to mineral oil is the risk factor in men. The Swedish population whose profession is to work in mineral oil resources showed a 57% increase in the occurrence of rheumatoid arthritis. APCA-positive individuals will develop rheumatoid arthritis in case of work exposure to silica. Other factors include lesser consumption of vitamin D and antioxidants and much more intake of sugar, sodium, red meats, proteins and iron which showed an increased risk of rheumatoid arthritis.

### c. Human microbiome:

The transfer from a symbiotic to a dysbiotic microbiome is the contributing risk factor for the development of rheumatoid arthritis as it is characterized by the extreme growth of the microbes and lack of bacteria/organisms. The outcome of this is liable for deviations in innate and adaptive immunity [9].

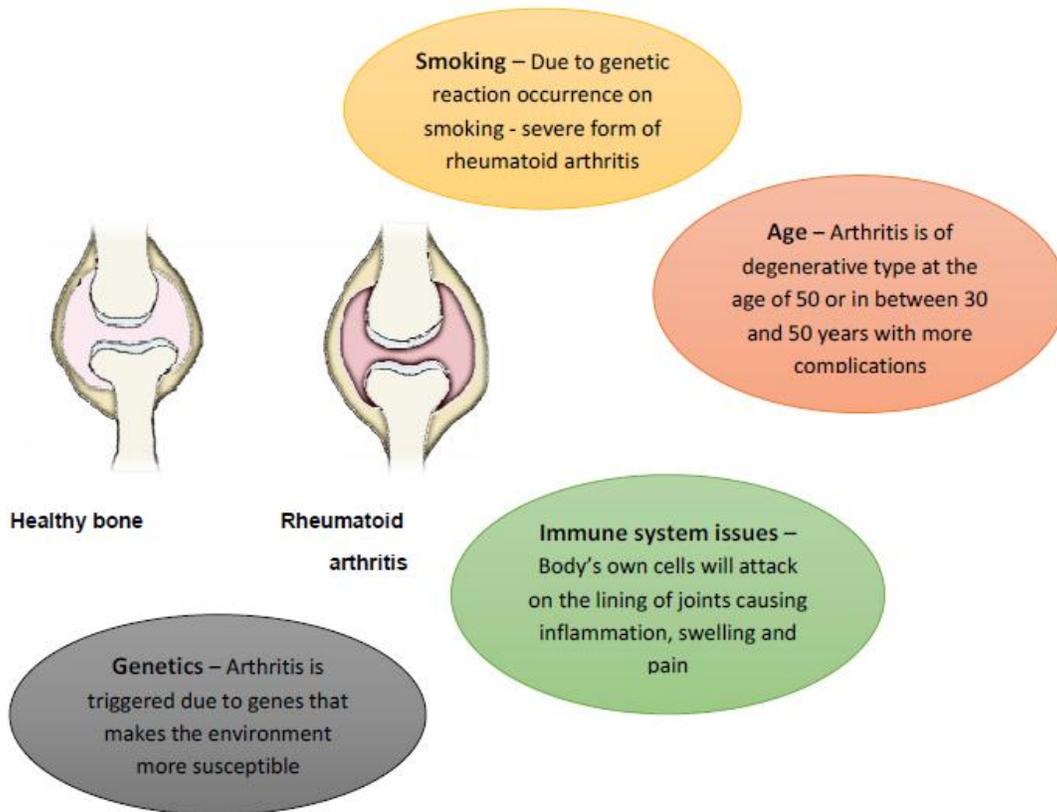


Fig. 2. Causes of rheumatoid arthritis

### 3. RISK FACTORS ASSOCIATED WITH RHEUMATOID ARTHRITIS

- **Environmental factors** like exposure of hormones, drinking of decaffeinated coffee more than 3 times a day, consumption of tobacco, smoking.
  - **Exposure of hormones:** In women, estrogens possess pro-inflammatory activity and androgens possess anti-inflammatory activity. Oestrogens effects differently on different immune cells (activation and suppression) that depend on the concentration of the serum, stage of reproduction or aging phase of the ovary, estrogen receptors expression or metabolism by the intracellular way. Oestrogen (HRT, Ocs) exposure, polycystic ovary syndrome, post-partum [10].
  - **Drinking coffee:** Consumption of coffee is a risk factor that triggers the release of rheumatoid factor. The factors correlated with the coffee consumption are age,

serum LDL cholesterol, smoking not dependently. The positive rheumatoid arthritis can be expected by the number of cups of coffee consumption. With smoking and coffee consumption, the occurrence of rheumatoid arthritis is more [11].

- **Consumption of tobacco:** Smoking (nicotine) causes a rise in the levels of oxidative stress in the human body which triggers the induction of rheumatoid arthritis. Smoking of cigarettes has increased the expression of matrix metalloproteinase-12 (MMP-12) (produced by macrophages and dendritic cells). Over expression of MMP-12 leads to the formation of the pannus, opaque synovium, macrophage infiltration is projecting and clear devastation of cartilages in the articules in the later stages [12].
- **Genetic factors** include gender (female), occurrence history in the family, elder age and HLA genotype.

- The risk of rheumatoid arthritis can be reduced with higher consumption of vitamin D, tea, oral contraceptives and breast-feeding.

#### 4. PATHOLOGY AND PATHOGENESIS

The initial abrasions in rheumatoid synovitis seem to be microvascular damage and the raise in synovial lining cells (seen laterally with perimysial infiltration with mononuclear cells). The examination through a microscope shows certain characteristic features like hyperplasia and hypertrophy of the cells in the synovial lining. The main or sectional variations in the vascular changes (includes embolism, ventricular damage and the development of new blood vessels where there is an impaired supply of blood in the region of trauma), dropsy and penetration with mononuclear cells (lymphocytes, monocytes, and immature granulocytes). The endothelial cell of rheumatoid synovium shows high endothelial venules of lymphoid organs. This is altered with exposure of cytokine to improve the penetration of the cells into the tissues which results in the nonstop rise in the number of linkage molecules (involved in this process). The size and the composition of the mononuclear cells may vary with the collections. The prime penetrating cells are T lymphocytes. These cells in the synovium of the rheumatoid are composed of CD4+ memory T cells, these cells form an accumulation of majority of cells all over the place in the veins of postcapillary. CD8+ T cells are distributed all over the tissues. In spite of the growth of T cells, rheumatoid synovitis is characterized by the penetration of numerous B cells and plasma cells that produce antibodies. Immune complexes are formed locally due to the fabrication of polyclonal Ig and autoantibody (rheumatoid factor) inside the synovial tissue. The rise in the number of mast cells in its activated state was observed in the rheumatoid synovium which releases few contents from their granules results in the inflammation locally. The synovial fibroblasts show a clear indication of the production of a number of enzymes (like collagenase and cathepsins) that will destroy the articular matrix components. The major site of erosion of the bone is osteoclast.

#### 5. SIGNS AND SYMPTOMS

Approximately 1% of the world population with some variability in the regions is affected by rheumatoid arthritis. This disease is high in

Native Americans like Chippewa Indians (~6%) and is shown lesser in Japanese, Chinese and Saharan blacks. Wrists, fingers, feet, elbows, ankles and knees and other parts of the body like shoulders, hips and cervical spine are affected with rheumatoid arthritis. Symptoms of the disease are passive movement pain, swelling, heat sensation, firmness in the mornings lasting for greater than an hour. Spindle-shaped fingers are often observed. All the above-mentioned symptoms will last for greater than 6 weeks and are diagnosed with rheumatoid arthritis.

Rheumatoid arthritis is often demonstrated with rheumatoid nodules which are extravascular indications. White cells and a radiating palisade of connective tissue have a central necrotic core which is located in the hypodermis on the stretching surfaces of fingers and elbows. Nodules are often observed in the other parts of the body like the scalp, back, feet, hands, buttocks or knees, heart valves, pericardium, parenchyma of lungs and spleen.

Myocardial infarction, stroke, Raynaud's phenomenon and rarely skin ulcers appear due to vascular insufficiency in the region of periphery occurs due to thrombosis of blood vessels. Systemic indications of rheumatoid arthritis are lethargy, melancholy, thinness, lymphitis, clinical depression, abnormal enlargement of spleen, weakness of the muscles, white nails, faster heartbeat, fever (origin is unknown). Ocular identifications are scleritis, anterior scleritis (evolve bluish color and painful) and posterior scleritis (Grave's disease or hyperthyroidism, oozing of choroid and vision loss) [13].

#### 6. CLINICAL COMPLICATIONS

1. **Depression** - With the use of corticosteroids, a population of 40% is affected. Some of the features are allied with depression are socioeconomic factors (pay, education, job, race, circumstances of the neighborhood), factors of patients (sex, age, ethnicity, concomitant, social support) and rheumatoid arthritis disease factors (injury, activity of the disease, pain, frailty, clinical reduction) [14].
2. **Infection** - may be caused either by rheumatoid arthritis or immunosuppressant use. The use of biologics may lead to severe infections along with the use of steroids, DMARDs [15].

3. **Malignancy** – Lymphoma (the risk is doubled in rheumatoid arthritis patient), Lung cancer (causes- smoking, interstitial disease of lungs), Skin cancer (synergistic effect of risk with the use of immunosuppressant's).
4. **Cardiovascular disease** – The risk associated with rheumatoid arthritis regarding cardiovascular diseases is heart failure, ischaemic heart disease, myocardial infarction, and coronary revascularization [16].

## 7. DIAGNOSIS

Findings of typical examination include swelling, waterlogged, compassion, and heat, shrinkage of muscles nearby the joints involved.

- Initial tests of the laboratory include differential rheumatoid factor and sedimentation rate of the erythrocytes or proteins which are C reactive in nature.
- Occasionally aspiration of the joint may be required (in case of monoarticular presentations to overcome infectious or crystal-induced arthritis).
- Renal and hepatic baseline function tests (for the choice of medications to be made)

- Positive predictive value and higher specificity can be achieved by the antibody of an anti-cyclic citrullinated peptide (This antibody is present in less than 60% of the rheumatoid arthritis patients) [17].

## 8. TREATMENT

- Treatment of rheumatoid arthritis requires patient's knowledge regarding the disease.
- Treatment for rheumatoid arthritis includes 3 approaches – NSAIDs and glucocorticoids administered intra-articularly or orally (low dose), DMARDs and biologics.
- **NSAIDs** - Reduce pain in the joints and swelling (the disease course is not altered). **Indication:** Do not use alone.
- **Steroids** – Symptoms are relieved and joint damage is slowed down. **Indication:** Should be prescribed at lower doses for a short period of time (bridge therapy). [Calcium+Vitamin D oral supplements – limit bone demineralization].
- **DMARDs** – Reduces the progress of the disease and advances overall long term prediction.
- **Biologics** – Target cytokines, signaling molecules and inflammatory cells and demolition of the joints.

**Table 1. List of DMARDs used to treat rheumatoid arthritis [14]**

Sl. no	Drug	Dose
1	Sulfasalazine	2-3 g daily
2	Etanercept	25 mg twice/week or 50mg sc weekly
3	Methotrexate	15 mg/week
4	Adalimumab	40 mg (biweekly)
5	Cyclosporine	2.5-5 mg/day

**First-line agents:** Adalimumab, etanercept, infliximab

**IL-1 Antagonist:** Anakinra

**Anti-Bcell antibody:** Rituximab

**Down-regulator of T-cell co-stimulation:** Abatacept

**Disadvantages:** Risk of infection is more, tuberculosis may be reactivated [18].

## 9. SURGERY

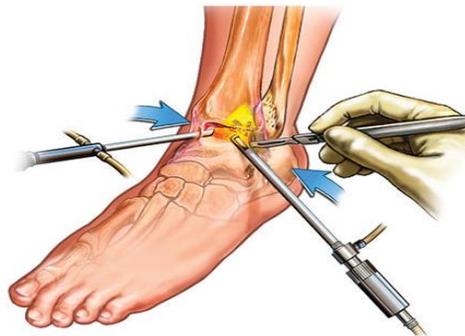
- **Synovectomy:** The injured lining of the joint is removed by surgery is performed on the knees, elbows, wrists, fingers, and hips [19].



**Fig. 3. Arthroscopic synovectomy (removal of synovium damaging the joints by inserting a miniature camera) of wrist (B) Wrist joint diffuse synovectomy (C) Removal of synovium successively**

Source: [https://www.researchgate.net/figure/A-Arthroscopic-synovectomy-of-the-wrist-rheumatoid-arthritis-B-Intraoperative\\_fig1\\_273185482](https://www.researchgate.net/figure/A-Arthroscopic-synovectomy-of-the-wrist-rheumatoid-arthritis-B-Intraoperative_fig1_273185482) (Accessed on 10 June 2020)

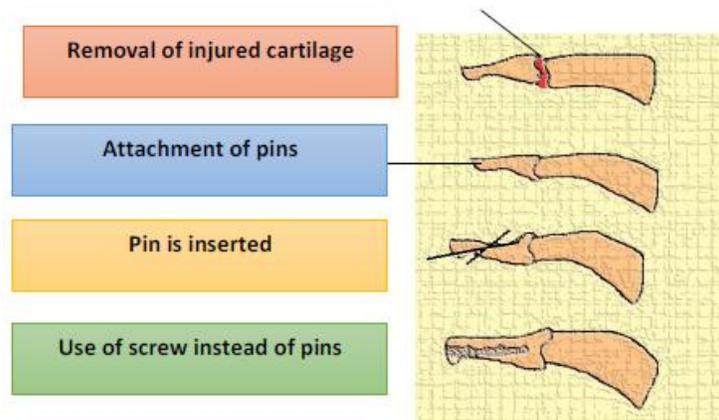
- **Repair of tendon:** The tendons around the joints will slacken or break due to tenderness and destruction of the joint and the joints around the dented joints are repaired.



**Fig. 4. Ankle ligament reconstruction**

Source: <https://murdochorthopaedic.com.au/our-surgeons/peter-ammon/procedures/ankle-arthroscopy-ankle-ligament-reconstruction/> (Accessed on 10 June 2020)

- **Fusion of joint:** For the purpose of realignment or stabilization of the joint and relieving from the pain, the joints are fused.



**Fig. 5. Fusion of arthritic dip point in fingers**

Source: <https://centralcoastortho.com/patient-education/finger-fracture-fixation/> (Accessed on 10 June 2020)

- **Replacement of the total joint:** The dented parts are removed from the joint and fake thing made of metal and plastic was inserted [20].



**Fig. 6. Knee joint replacement**

Source: <https://www.houstonhipandkneesurgeon.com/less-invasive-knee.html> (Accessed on 10 June 2020)

## 10. THERAPY

- The therapist will suggest to perform certain exercises to retain the flexibility of the joints.
- Daily tasks to be performed by the patients.
- For the purpose of preventing stress on the joints which are painful, assistive devices are provided.
- A hand gripped kitchen knife will help to protect the finger and joints of the wrist [21]

## 11. LIFESTYLE AND HOME REMEDIES

- Regular exercises
- Heat or cold application
- Relaxation [21]

## 12. APPLICATIONS

- Since 1000-3000BC, bee venom therapy is used for the treatment of certain diseases

used in oriental traditional medicine. In BVT, bee's venom is applied directly or given through injection. BVT possesses anti-inflammatory, anti-necrobiosis, anti-myelofibrosis and anti-arteriosclerosis effects. In oriental medicine, BVT was preferably used for treating pain and inflammatory diseases. Recently, BVT is also used to treat parkinsonism, Lou Gehrig's disease, and other circulatory diseases. (Major constituents of bee venom are apamine, mast cell degranulating peptide, phosphatidylcholine 2-acyl hydrolase 1B, honey bee melittin, apamin, and Hyazyme) [21].

- Hydrogels (Aspasomes) are transdermal delivery systems to treat rheumatoid arthritis [22].
- Biomarkers (leptin, resistin, IL-6 etc) [23].
- Anti-citrullinated protein antibodies [24].

## 13. PATENTS ON DIAGNOSIS AND TREATMENT FOR RHEUMATOID ARTHRITIS

**Table 2. List of patents for treatment and diagnosis of rheumatoid arthritis**

SI no.	Patent no.	Invention	Author	Year of publication	References
1	3852454	The present invention focuses on treating rheumatoid arthritis with 5-mercaptopyridoxine or its disulfide form, salt form, pyriothoxine form. From past studies, aspirin is used as an anti-inflammatory agent only in case of acute conditions. The	Jaffe I	1974	[25]

SI no.	Patent no.	Invention	Author	Year of publication	References
		formulation was administered rectally, orally (lozenges, elixirs, troches, tablets, suspensions, powders or granules in dispersable form, emulsions, capsules or syrups), parenterally (subcutaneous, intravenous, intramuscular, intrasternal injections or by infusion) or by inhalation. For a novel method of treatment, the prescribed dose is 1-100 mg/kg and the general dose is 5-50 mg/kg. Oral route of administration dosage is 5mg-5g.			
2	4746662	The compound used in the treatment of rheumatoid arthritis is 3,5-dichloromethotrexate which is also used in the treatment of cancer under the class antimetabolite. This compound can suppress injury and devastation of the joints which are in collaboration with arthritis in mammals or animals with warm-blooded in nature. A combination therapy gives synergistic effects for treating arthritis on post administration of leucovorin.	Kerwar, Suresh S., Sloboda, Adolph E	1988	[26]
3	US4732757A	By using immunization by passive method against bacterial spectrum causing infections that host on the gastrointestinal tract of the humans. In order to inoculate the cattle of the dairy, an exclusive amalgamation of species of bacteria were verbalized into a vaccine. The milk obtained from the vaccinated cattle possesses IgG antibody which acts against the spectrum of microbes.	Ralph J. Stolle, Lee R. Beck	1988	[27]
4	5723503	This invention tells about the therapeutic quantity administration of derived molecules or mononuclear cells that are allogenic in nature. The mononuclear cells used are white blood cells (26pprox.. 80-100 million cells) are administered as a standard buffered salt solution for an interval of 6-8 weeks will produce beneficial effects.	Smith, Bruce J, Fort, John G	1998	[28]
5	WO9962528	The invention gives the data on treating the symptoms of arthritis by using the Ngali Nut oil extract. The extract is administered alone or in combination with other agents that are therapeutically beneficial for topical use. The combination may	Hull, Peter, Hugh	1999	[29]

SI no.	Patent no.	Invention	Author	Year of publication	References
		include the drugs which are compatible in nature. Reapplication of the oil depends on the rigorousness of the symptoms of rheumatoid arthritis.			
6	5908628	The invention involves the combination of analgesic, anti-inflammatory, and antipyretic properties to treat rheumatism. The composition will include filth of silkworm and some herbal roots.	Hou, Liping	1999	[30]
7	US20040006038	The essential therapy to treat rheumatoid arthritis is the invention of artificially inhibiting the intracellular signals of the c-fos product of the gene. Furthermore, the c-fos gene acts as a factor of transcription that binds to sites of rheumatoid arthritis genes (AP-1 sites). To inhibit such bindings for the signaling of the c-fos product, the oligonucleotide is provoked. A double-stranded oligonucleotide composed of the sequence of 5'-tgagtca-3' is administered to the patient with rheumatoid arthritis.	Shiozawa, Shunichi	2004	[31]
8	US20090252692	In the prophylaxis of the treatment of rheumatoid arthritis (of various types) and other conditions with inflammatory joint, diseases of the gum, psoriasis can be treated with the composition consisting of lecithin, olive oil, fatty acids which are esterified and tocopherols which are mixed in nature in order to minimize the risks associated with the well-known managements.	Spencer, William P	2009	[32]
9	US2010190755	The invention involves treating rheumatoid arthritis by administering tetracycline. Prior to the direct administration, tetracycline is converted into its salt, ester or prodrug form.	Abato; Paul; Bowser; Todd; Higgins; Paul; Verma; Atul K; Zhang-Hoover; Jie	2010	[33]
10	US20110039928	To treat the injured or inflamed joints, a composition treatment consisting of anti-inflammatory composition. The composition can be administered either orally or topically.	Golini, Jeffrey M.	2011	[34]
11		In this invention, a device (microneedle, a variety of nanostructures invented on the surface) is used which permeates across the dermal barrier with a pattern. The form of the drug used in	Ross, Russell Frederick	2013	[35]

SI no.	Patent no.	Invention	Author	Year of publication	References
		the device (microneedle) may be in fluid form.			
12	WO2015177097	Rheumatoid arthritis can be treated which includes a reduction in DAS28-CRP and a rise in the patient population with a clinical benefit can be determined by ACR 20, ACR 50 and ACR 70.	Close David, Godwood Alex, Hopton Mark	2015	[36]
13	US20170350884	The invention involves the method for developing a tool to detect cathepsin A by using the samples of the urine of patients which may provide a method of diagnosis for treating rheumatoid arthritis. Also, a kit of biomarkers is developed for the purpose of diagnosis of osteoporosis in a patient possessing rheumatoid arthritis.	Wan-Uk Kim, Daehee Hwang, Yune-Jung Park, Sung Yong You, Seung-Ah Yoo	2017	[37]

**Table 3. List of marketed products of drugs used in the treatment of rheumatoid arthritis**

Sl. no	Brand name	Drug	Formulation	Drug class	Reference
1	Otrexup	Methotrexate	Injection (SC)	Antimetabolites Antirheumatics Antipsoriatics	[38]
2	Celebrex	Celecoxib	Tablet	COX-2 Inhibitor	[39]
3	Plaquenil	Hydrochloroquine	Tablet	Antirheumatics Antimalarial	[40]
4	Mobix G Spray	Meloxicam	Spray	Non-steroidal anti-inflammatory drugs	[41]
5	Humira	Adalimumab	Biologic	Antirheumatic TNF- $\alpha$ inhibitor	[42]
6	Actemra	Tocilizumab	Injection (IV)	IL Inhibitors	[43]
7	Arava	Leflunomide	Oral	DMARD Immunosuppressant	[44]
8	Remicad	Infliximab	Injection (IV)	Antirheumatic TNF- $\alpha$ Inhibitors	[45]
9	Orencia	Abatacept	Injection (IV)	Antirheumatic Immunosuppressant	[46]
10	Norco	Acetaminophen/ Hydrocodone	Tablet	Narcotic analgesic combinations	[47]

**Table 4. List of targeted delivery systems**

Sl. no	Targeting agent	Receptor	Delivery systems	Drug	References
1	Folic acid	Folate receptors	Liposomes Dextran Albumin Chitosan	Methotrexate Methotrexate Etoricoxib IL-1Ra DNA	[50] [51] [52] [53]
2	RGD	Integrin receptor	PEG liposomes Nanoparticles of gold half shell PLGA	Dexamethasone phosphate Methotrexate	[54] [55]

**Table 5. List of reviews of patient compliance**

Sl. no	Drug	Patient compliance	Patient incompliance	Reference
1	Certolizumab pegol (Cimzia)	Works best and fast in treating rheumatoid arthritis Reduction of pain Fast relief from rheumatoid arthritis Movement of hands without pain and stiffness	Raise in blood pressure (occurrence 1 in 100) Reappearance of psoriasis, hive-like reaction on mouth and cheeks Stomach upset, pain in the abdomen and muscles, development of thyroid nodules, shrinkage of spleen, enlarged liver Weight gain	[56]
2	Adalimumab (Humira)	No side effects even after use for 8 years Biweekly dose will work well	Headache after taking injection Depression, vertigo, tinnitus, withdrawal on usage of Benzos Pain and respiratory symptoms	[57]
3	Tocilizumab (Actemra)	Infusions will treat in a better way if taken 5 weeks once, improvement in blood levels No stiffness is observed	Swelling of lower leg, popping up of blisters due to chemical eruption (due to actemra infusion) Severe nausea, morning sickness, puffiness of the face, swelling of legs, discomfort in the hip and knee joints, rigidity of belly Constricted breathing, dizziness, headache, fatigue	[58]
4.	Methotrexate	With a double-fold increase in the quantity of folic acid, the activity of methotrexate is enhanced.	Diarrhea (24-48hrs after intake) Headaches, bruising on contact with wounds Hair fall, severe stomach pains, swallowing difficulties Nausea, fatigue, malaise	[59]

#### 14. CURRENT TRENDS

1. **Nanoparticle system** is used in the treatment of rheumatoid arthritis. The nanoparticle system includes bovine lactoferrin saturated with iron, solid lipid nanoparticles, nanoparticles of hyaluronan, nanoparticles of polyethylene amine super magnetic iron oxide, tranilast loaded nanoparticles, chitosan loaded nanoparticles, nanoparticles loaded with thiolated glycol chitosan, nanoparticles of perfluorocarbon [48].
2. **Opioid therapy** for short-term and long-term rheumatoid arthritis. Opioid therapy includes drugs such as morphine sulfate and tramadol (>6 weeks), opioids except for tramadol (4 weeks – oral or transdermal) [49].
3. **Targeted delivery systems:** In this system, different targeting agents were selected for different receptors and delivery systems.

#### 15. CONCLUSION

Rheumatoid arthritis is a chronic autoimmune disease with the characteristic features of the destruction of synovium, cartilage and joints. Environmental and genetic factors play an important role in the development of rheumatoid arthritis with occurring pathological events. Many developments have been made to treat the disease and also the diagnosis of the disease. Surgeries are performed to remove the inflammation-causing agent (cytokines). Certain marketed formulations along with their classes have been enlisted in the table. Recent trends for treating the disease was explained in brief. To avoid arthritis or in the management of arthritis, a healthy diet should be followed along with exercising.

#### DISCLAIMER

The products used for this research are commonly and predominantly use products in our

area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

### ACKNOWLEDGEMENT

The authors thank M. S. Ramaiah University of Applied Sciences for providing the necessary facilities.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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