Rheumatoid Arthritis: A Comprehensive Review of Etiology, Diagnosis, and Therapeutic Interventions

Poonam Yadav[1], Neeraj Kumar[2], Kusum Lata[3], Sachin Katri[4], Sachin Kumar[5]

[1]Department of Pharmacology, School of Healthcare & Allied Sciences, GD Goenka University, Sohna-Gurgaon Road, Sohna, 122103, Haryana, India.
[2,3,4,5]Department of Pharmaceutics, School of Healthcare & Allied Sciences, GD Goenka University, Sohna-Gurgaon Road, Sohna, 122103, Haryana, India.

***Corresponding author: Poonam Yadav,**
Department of Pharmacology, School of Healthcare & Allied Sciences, GD Goenka University, Sohna-Gurgaon Road, Sohna, 122103, Haryana, India. E-mail: poonamyadav98958@gmail.com

Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily affects the joints, causing inflammation, pain, and stiffness. The immune system of those people's attacking healthy tissues, particularly the synovium, a membrane that lines the joints. The body's immune system mistakenly identifies the synovium as a threat and starts attacking it. This immune response leads to inflammation, which can eventually damage cartilage, bones, tendons, and ligaments within the joint. It's a progressive disease, which damage worsens over time if left untreated. Early diagnosis and appropriate management are crucial in preventing severe joint damage. Untreated or poorly controlled rheumatoid arthritis can lead to complications like joint deformities, loss of joint function, and disability. RA can also affect other organs, leading to systemic complications such as cardiovascular issues and lung problems. If someone is experiencing symptoms suggestive of rheumatoid arthritis, it's crucial to seek medical attention for a proper evaluation and diagnosis. Early diagnosis and appropriate treatment can significantly improve long-term outcomes and help manage the impact of the disease on daily life. The goal of RA treatment is to relieve symptoms, reduce inflammation, prevent joint damage, and improve quality of life. Treatment options often involve a combination of medications (such as disease-modifying antirheumatic drugs - DMARDs, biologics, and corticosteroids), physical therapy, and lifestyle changes.

Keywords: *Rheumatoid arthritis, Inflammation, DMARDs, Methotrexate, Corticosteroids*

1. Introduction

An autoimmune allergy disease called rheumatoid arthritis (RA) results in persistent inflammation and synovial fibroblast proliferation, which ultimately causes atherosclerosis and the irreversible loss of articular cartilage and bone [1]. Although the precise mechanism is still unknown, inflammation-induced loss of articular cartilage is the main cause of RA. The same may result in symptoms like fatigue, weight loss, joint pain and swelling, stiffness in the joints, sleeplessness, and flu-like symptoms [2]. Consequently, difficulties with daily activities such as dressing, grooming, walking, and cooking are common. Furthermore, fatigue and discomfort can often negatively impact social life and make it difficult to work [3]. Globally, the percentage of people with RA varies between 0.5 and 1%, while in India, over 20% of people have arthritis of some kind [4]. Women (4%) experience it more frequently than men (2%). In affluent countries, more than half of RA patients quit their full-time jobs ten years after the disease first appeared. One in every 100,000 individuals is diagnosed with RA each year, and 1.3 million people in the US suffer from the condition. When the illness has worsened over the course of two years, diagnosis can be made at any point between three months after it first appears and two years later [5].

Joints are the main organs affected by rheumatoid arthritis (RA), a chronic inflammatory disease. As an autoimmune disorder, it causes inflammation in the joints when the immune system unintentionally targets the body's own tissues. Inflammation can lead to discomfort, edema, stiffness, and joint degeneration and deformities over time Some characteristics of rheumatoid arthritis consist of symmetrical joint involvement in which rheumatoid arthritis (RA) usually affects the wrists, knees, and fingers, among other joints on both sides of the body [6]. Even morning stiffness occurs in individuals with RA frequently have morning stiffness, especially after periods of inactivity. Inflamed joints may experience tenderness and pain. RA can result in a generalized sense of malaise and weariness. RA can cause problems in organs such as the skin, eyes, lungs, and heart as well as other areas of the body. Rheumatoid arthritis is thought to be caused by a mix of environmental and genetic factors, while the precise cause is unknown. The management of symptoms and prevention of long-term joint damage depend heavily on an early diagnosis and proper treatment [7].

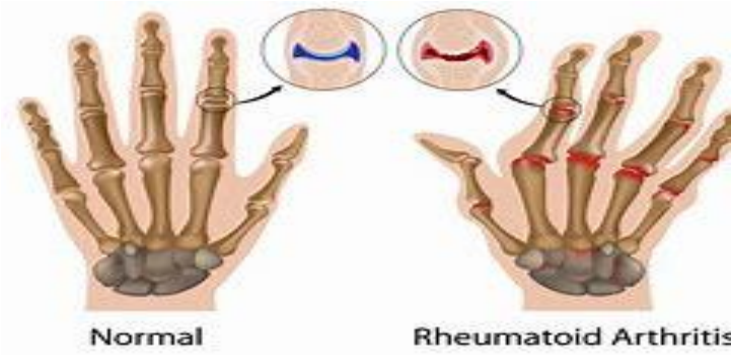

Figure 1. Joints difference in disease case

A variety of treatments, including nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and, in certain situations, biologics, are frequently used in combination to treat rheumatoid arthritis. The illness can also be effectively managed with physical therapy and lifestyle changes, such as consistent exercise and a nutritious diet. It's crucial that people who have symptoms that could indicate rheumatoid arthritis speak with a medical expert[8].

2. Common types of arthritis

There are various kinds of arthritis, and each has unique traits, causes, and therapies. These are a few typical kinds:

1. The most common type of arthritis is osteoarthritis (OA): It happens when the cartilage that shields and cushions the ends of bones ages. While it can affect any joint, the knees, hips, hands, and spine are the most frequently affected. Osteoarthritis, also known as "wear and tear" arthritis, is frequently linked to aging [9].
2. Rheumatoid arthritis (RA): As was previously established, rheumatoid arthritis is an inflammatory illness in which the synovium—the membrane lining the joints—is attacked by the immune system. Joint injury and inflammation may result from this. Both sides of the body's joints are frequently impacted by RA.
3. Psoriatic Arthritis (PsA): Some individuals with psoriasis, a persistent skin disorder, also have psoriatic arthritis. Along with the psoriasis-specific changes to the skin and nails, it might result in joint discomfort, stiffness, and swelling.
4. Ankylosing spondylitis(AS): One type of inflammatory arthritis that mostly affects the spine is called ankylosing spondylitis. Vertebral inflammation can result in pain and stiffness in the spine. The spine may fuse because of it over time [10].
5. Gout: Gout is defined by urate crystal buildup in the joints, which causes excruciating pain and inflammation. Although it can affect other joints as well, the big toe is typically affected. Elevated blood uric acid levels are linked to gout.
6. Lupus Arthritis: An autoimmune condition known as systemic lupus erythematosus, or SLE, can damage several organs, including the joints. Stiffness, edema, and discomfort in the joints can be symptoms of lupus arthritis.
7. Juvenile Idiopathic Arthritis (JIA): Children under the age of sixteen are susceptible to this group of arthritic diseases. There are multiple subtypes within it, and each has unique symptoms and traits.
8. Reactive arthritis: When an infection occurs in one area of the body, arthritis of the other develops in reaction. Usually, it affects the urinary tract, eyes, and joints.
9. Sjögren's Syndrome: Sjögren's syndrome is mostly an autoimmune disease that affects the glands responsible for saliva and tears, but it can also cause joint discomfort and inflammation [11].

3. Risk factors for rheumatoid arthritis

Joints are the main organs affected by rheumatoid arthritis (RA), a chronic autoimmune disease. Although the precise etiology of RA remains incompletely understood, a number of established risk factors have been linked to the illness's

development. It's crucial to remember that a person's chance of developing rheumatoid arthritis is not increased by the presence of one or more risk factors. It is likely that a combination of lifestyle, environmental, and genetic factors contribute to the total risk [11].

The following are some typical risk factors for rheumatoid arthritis: An increased chance of developing rheumatoid arthritis is associated with a family history of the condition. The HLA-DRB1 gene is one genetic marker that has been connected to an increased risk of RA. Rheumatoid arthritis is more common in women than in men. Hormonal factors may contribute to this gender gap, though the exact causes are unknown. Although rheumatoid arthritis can strike anyone at any time, it usually starts in the 40s to 60s [12]. Rheumatoid arthritis may develop because of exposure to specific environmental factors. Cigarette smoke, air pollution, and occupational exposure to specific dust and fiber types are a few examples of these factors. Rheumatoid arthritis may develop because of hormonal changes, especially in women. For instance, the onset of RA is frequently linked to menopausal and pregnancy-related hormonal changes [13]. In people who are genetically predisposed to the illness, some infections, such as specific bacterial or viral infections, may cause the onset of rheumatoid arthritis. Since being overweight can aggravate joint inflammation and stress, there is some evidence that obesity may raise the chance of developing rheumatoid arthritis. It is commonly known that smoking poses an environmental risk for developing rheumatoid arthritis. It tends to exacerbate the disease as well as raise the chance of getting RA. Rheumatoid arthritis risk has been linked to poor oral health, particularly periodontal (gum) disease. If there is a genetic predisposition, joint trauma or injuries may raise the chance of developing rheumatoid arthritis [14].

It is noteworthy that although these variables are linked to a higher likelihood of developing rheumatoid arthritis, their existence does not ensure the onset of the illness. On the other hand, rheumatoid arthritis can still strike people who do not have these risk factors. Furthermore, further investigation is probably going to provide more information regarding the intricate interactions among variables that lead to the onset of rheumatoid arthritis. It is best to speak with a healthcare provider for specific advice and information if you have questions about rheumatoid arthritis or its risk factors [15].

4. Rheumatoid arthritis causes

The precise etiology of rheumatoid arthritis (RA), an autoimmune disease, is unknown. The immune system of the body, which is meant to defend against foreign invaders like bacteria and viruses, can malfunction and attack its own tissues, leading to autoimmune diseases. The synovium, the lining of the membranes surrounding the joints, is the target of the immune system in the case of RA [16].

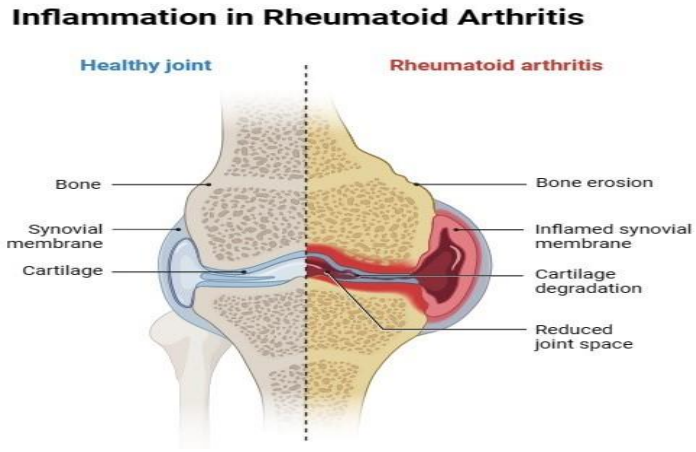

Figure 2. Compared healthy joint with rheumatoid arthritis.

Rheumatoid arthritis is thought to be caused by a mix of hormonal, environmental, and genetic factors, though the exact cause of the condition is still unknown. The following elements are believed to be involved. Rheumatoid arthritis has a significant hereditary component. An elevated risk of developing RA is linked to specific genetic markers, most notably variations of the HLA-DRB1 gene. But not everyone who carries these genetic markers gets the illness, indicating that other factors might also be involved. The immune system misinterprets the body's own tissues as foreign invaders and launches an attack on them in autoimmune diseases such as RA. The synovium is the main target of RA, which causes inflammation and joint damage [17]. In people who are genetically predisposed to the condition, several environmental factors may cause or worsen rheumatoid arthritis. For example, smoking is a known environmental risk factor for RA. In certain instances, exposure to specific infections—such as those caused by bacteria or viruses—may also have a role in the disease's development. Rheumatoid arthritis has been associated with hormonal fluctuations, especially in women. The disease frequently begins in the reproductive years, and changes in hormones related to menopause and pregnancy may have an impact on its course [18]. Rheumatoid arthritis is characterized by persistent inflammation. Inflammatory chemicals are released because of the immune system attacking the synovium, and these chemicals aggravate and worsen joint pain and swelling. Rheumatoid arthritis patients experience thickening and inflammation of the synovium. As a result, more synovial fluid is produced, which may result in joint swelling. The degeneration of bone and cartilage in the joint is also facilitated by the activated synovial cells [19]. The inflammatory process in rheumatoid arthritis is significantly influenced by certain proteins known as cytokines. In the joints of people with RA, cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) are overproduced, which leads to inflammation and joint damage. It is noteworthy that the onset of rheumatoid arthritis is probably impacted by a multifaceted interaction of these variables, and the particular initiators may differ amongst individuals. Deepening our understanding of the fundamental causes of RA is the goal of ongoing research, which could eventually result in better treatments and preventive measures. For a comprehensive assessment and advice, it's best to speak with a healthcare provider if you're worried that you may have rheumatoid arthritis [20].

5. Symptoms of rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that primarily affects the joints, but it can also involve other organs and systems. The symptoms of rheumatoid arthritis can vary from person to person and may come and go. The disease typically involves periods of flare-ups and remissions. Common symptoms of rheumatoid arthritis include pain is a prominent symptom of RA and often affects multiple joints [21]. The pain is usually symmetrical, meaning that if one knee or hand is affected, the same joint on the other side of the body is often affected as well. Inflammation in the synovium, the lining of the joint, leads to swelling. This swelling can make the joints feel warm and tender to the touch. RA can cause joint stiffness, especially in the morning or after periods of inactivity [22]. Morning stiffness lasting for more than 30 minutes is a common characteristic of RA. Inflammation can cause the skin over the affected joints to become red. Many people with rheumatoid arthritis experience persistent fatigue, which can be unrelated to physical activity. This fatigue may be a result of the body's overall inflammatory response. Some individuals with RA may experience low-grade fevers, especially during flare-ups. Unexplained weight loss can occur in some cases of rheumatoid arthritis. Over time, if RA is not well-managed, joint deformities may develop [23]. This can include changes in the shape and alignment of the joints, particularly in the hands and feet. Rheumatoid nodules are firm lumps that can develop under the skin, usually around pressure points such as the elbows or fingers. Not everyone with RA develops nodules. Some individuals with RA may experience muscle pain, particularly around affected joints [24]. It's important to note that the severity and combination of symptoms can vary widely among individuals with rheumatoid arthritis. Early diagnosis and treatment are crucial for managing symptoms, preventing joint damage, and improving overall quality of life [25]. If you suspect you have rheumatoid arthritis or are experiencing joint pain and inflammation, it's important to consult with a healthcare professional for a proper diagnosis and appropriate management plan. Rheumatologists are specialists who diagnose and treat conditions like rheumatoid arthritis [26].

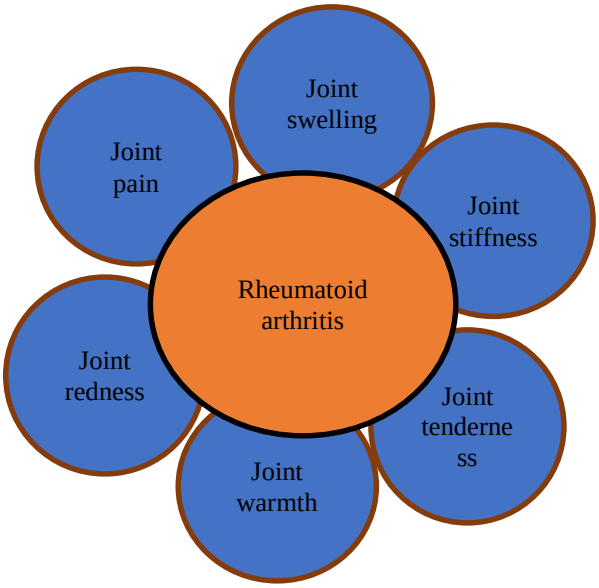

Figure 3. Symptoms appear in rheumatoid arthritis

6. Rheumatoid arthritis: Diagnosis and management

Although I am not a medical professional, I can give you some general information. Joints are the main organs affected by rheumatoid arthritis (RA), a chronic autoimmune disease. A combination of clinical assessment, medical history, and different diagnostic tests are used to diagnose RA [27]. The following are some standard procedures for diagnosing rheumatoid arthritis:

1. Physical examination and medical history: Your symptoms, their duration, and any family history of arthritis will be inquired about by the doctor. A comprehensive physical examination will be performed to look for warmth, soreness, and swelling in the joints.
2. Blood Tests: Rheumatoid Factor (RF): A positive result on an RF test is detected in certain RA patients, but it is not conclusive as it can also be found in some healthy individuals and people with other conditions. Antibodies against the cyclic citrullinated peptide, or anti-CCP antibodies, are more specifically directed against RA. Increased body inflammation is indicated by elevated levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [28].
3. Imaging Studies: X-rays: These can show alterations in the condition of joints over time. Magnetic Resonance Imaging (MRI): This modality can assist in determining the extent of joint inflammation and offers fine-grained images of soft tissues.
4. Analysis of Synovial Fluid: Extracting synovial fluid from a symptomatic joint can assist in identifying whether inflammation is brought on by RA or another factor.
5. Clinical Criteria: Based on the quantity and duration of symptoms, the American College of Rheumatology (ACR) has developed criteria for classifying RA.
6. Joint Ultrasound: This imaging modality allows for the real-time visualization of joint damage and inflammation [29].

It's crucial to remember that no one test can definitively diagnose rheumatoid arthritis; instead, a combination of these factors is frequently used. To manage RA and avoid joint damage, early diagnosis and treatment are essential. It is imperative that you speak with a healthcare provider for a proper evaluation and diagnosis specific to your circumstances if you think you may have RA or are exhibiting symptoms [30].

7. Treatment

Rheumatoid arthritis (RA) is usually treated with a multidisciplinary approach that may include lifestyle modifications, medication, and, in certain cases, surgery. Relieving symptoms, reducing or preventing joint damage, enhancing overall well-being, and improving function are the main objectives of RA treatment. It's critical that RA patients collaborate closely with their medical team to create a customized treatment strategy [31]. The following are some typical elements of RA treatment:

1. Drugs: Disease-Modifying Antirheumatic Drugs (DMARDs): These drugs, which include sulfasalazine, methotrexate, and others, work to change or slow down the disease's course. Certain immune system components implicated in the inflammatory process are targeted by biologics, such as tumor necrosis factor (TNF) inhibitors (e.g., etanercept, adalimumab). Drugs like tofacitinib function by preventing the action of enzymes that are necessary for the immune response. During flare-ups, a doctor may prescribe the short-

term use of steroids like prednisone to lessen inflammation. Modifying Disease One class of drugs called antirheumatic drugs (DMARDs) is used to treat autoimmune diseases, including rheumatoid arthritis (RA) and other conditions involving inflammation of the joints [32]. Instead of only treating symptoms, these medications seek to alter the underlying disease process and slow down the progression of these illnesses. DMARDs fall into two main categories are biologic DMARDs (bDMARDs) and conventional synthetic DMARDs (csDMARDs). csDMARDs, or conventionally synthetic DMARDs: Methotrexate: For rheumatoid arthritis, this is frequently the first line of treatment. It aids in lowering inflammation and immune system suppression. Leflunomide, hydroxychloroquine, and sulfasalazine are additional csDMARDs that can be taken on their own or in conjunction with other medications [33]. Biologically based DMARDs were inhibitors of the tumor necrosis factor (TNF): etanercept, infliximab, and adalimumab are among them. They specifically target a protein that is involved in the process of inflammation. Interleukin-1 (IL-1) Inhibitors: One such drug is anakinra, which prevents the inflammatory mediator's effects. Inhibitors of interleukin-6 (IL-6): Tocilizumab is one example of an IL-6 inhibitor that targets IL-6, an inflammatory response mediator. Inhibitors of B cells: Rituximab is one example of an inhibitor that targets B cells, which are part of the immune response. T-Cell Inhibitors: One medication that modifies T-cell activity is abatacept. DMARDs reduce inflammation and avoid joint damage by altering or suppressing the immune system. Frequently, they are prescribed in tandem to maximize their efficacy. The severity of the illness, the patient's general health, and any possible side effects all play a role in the DMARD selection [34]. Compared to its parent molecule, MTX is a modified form of folate that is intended to have a higher binding affinity for dihydrofolate reductase (DHFR). When used alone or in conjunction with other DMARDs, MTX is the mainstay of treatment for RA. In the short term, MTX demonstrated a significant clinical and statistically significant benefit over a placebo in the treatment of individuals with RA, according to a recent meta-analysis [34]. However, the medication's use was linked to a 16% discontinuation rate because of unfavorable side effects. Also, patients in the MTX group had statistically significantly lower radiographic progression rates, as indicated by an increase in erosion scores of greater than three units. It has been suggested that MTX is involved in the processes of folate antagonism, adenosine signaling, inhibiting the production of methyl donors in reactive oxygen species, downregulating the expression of adhesion molecules, altering cytokine profiles, and downregulating eicosanoids and MMPs. Certain single nucleotide polymorphisms (SNPs) have been linked to MTX responsiveness, according to 83 genome-wide association studies (GWAS) and SNP analysis [35]. For instance, those found in the genes for solute carrier family 19 member 1 (SLC19A1), 5-aminoimidazole-4-carboxamide (ATIC), and gamma-glutamyl hydrolase (GGH). However, the studies' findings are contradictory, and more substantial genomic research is required to advance our knowledge. For RA patients, MTX is prescribed as a weekly low-dose (5–25 mg) regimen, with dosage determined by the severity of the condition and any side effects [36]. When administered orally, MTX has a more variable uptake and produces fewer significant side effects than when administered subcutaneously. When compared to oral MTX, subcutaneous MTX administration likewise showed a higher bioavailability. To optimize dosage and evaluate

85 MTX's hepatotoxic and immunosuppressive effects, frequent blood tests are needed, starting once a month. A few well-known medication interactions for MTX include pancytopenia-causing cotrimoxazole mixed with lung and liver problems-causing azathioprine or leflunomide. NSAIDs and MTX have been routinely used for over 30 years; therefore, they can be used safely together to control symptoms [37]. The evidence that MTX raises the risk of cancer above and beyond the elevated relative risk of neoplasia linked to RA itself is inconclusive. The total risk is minimal despite this. The development of accelerated nodulosis, also referred to as MTX-induced accelerated nodulosis (MIAN), is another adverse effect linked to MTX use. MIAN affects 1–10% of patients taking MTX [38].

2. Pain Relieving Drugs: Nonsteroidal anti-inflammatory drugs (NSAIDs) can lessen inflammation and relieve pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to treat rheumatoid arthritis (RA) to lessen inflammation and relieve pain. Even though NSAIDs don't stop the underlying course of RA, they can relieve symptoms and enhance a patient's quality of life. NSAIDs, like diclofenac, naproxen, and ibuprofen, are frequently prescribed to treat rheumatoid arthritis patients for pain and inflammation. These drugs function by blocking the activity of cyclooxygenase (COX) enzymes, which are involved in the synthesis of prostaglandins, which are responsible for pain and inflammation [39]. NSAIDs are commonly used in conjunction with disease-modifying antirheumatic medications (DMARDs), which attempt to alter the fundamental mechanism of disease in RA. NSAIDs relieve pain and swelling while DMARDs target the immune system to impede the progression of the disease. NSAIDs are frequently advised for use in the short term to treat acute symptoms, such as inflammatory and pain flare-ups. High doses of NSAIDs used over an extended period may raise the risk of adverse effects, such as cardiovascular events and gastrointestinal problems [40]. Proton pump inhibitors (PPIs) or other gastroprotective drugs may be prescribed by medical professionals in addition to NSAIDs to lower the risk of gastrointestinal side effects, such as bleeding and stomach ulcers. There is evidence linking certain NSAIDs to a higher risk of cardiovascular events. Patients who already have cardiovascular disease should talk to their doctors about the advantages and disadvantages of using NSAIDs. Age, comorbidities, overall health, and the existence of gastrointestinal or cardiovascular risk factors are among the factors that influence the choice of NSAID and the length of time a patient uses it. It's crucial to monitor patients regularly and follow up with a healthcare professional to evaluate the efficacy of treatment and handle any possible side effects. Rheumatoid arthritis patients should collaborate closely with their medical team to create a comprehensive treatment plan that takes both symptomatic relief and disease modification into account. This could entail a mix of DMARDs, NSAIDs, and other drugs depending on the person's unique requirements and health condition [41].

3. Shifts in Lifestyle: Workout regimens intended to increase range of motion, strength, and joint function. Assists people in learning how to protect their joints while performing daily tasks. It's crucial to strike a balance between exercise and rest, and joint protection methods can lessen the strain on harmed joints. Although there isn't a single diet that can treat RA, maintaining a balanced, healthful diet may improve general wellbeing. Some

people discover that incorporating antioxidants and omega-3 fatty acids into their diet can help lower inflammation [42].

4. Surgery: Surgery may be an option if there is significant joint deformity or damage. Surgery for joint replacement.

5. Observation and Frequent Examinations: It's crucial to schedule follow-up visits with medical professionals on a regular basis to track the disease's development and modify treatment as necessary [43]. It's critical that people with RA be open and honest with their medical team about their symptoms, worries, and any drug side effects. Depending on how a patient responds to therapy and how the disease progresses over time, treatment plans may need to be modified. Effective RA management and the reduction of long-term joint damage depend on early diagnosis and intervention [44].

8. Pathophysiology of Rheumatoid arthritis

The chronic autoimmune disease known as rheumatoid arthritis (RA) is typified by inflammation of the synovium, which is the lining of the membranes surrounding the joints. A complex interaction between genetic, environmental, and immune system factors is involved in the pathophysiology of RA [45]. The following are the main elements of rheumatoid arthritis's pathophysiology: Genetic Elements because RA typically runs in families, there is a genetic predisposition to the condition. There is a genetic marker called HLA-DRB1 that is linked to a higher chance of developing RA. In people with a genetic predisposition, environmental factors can precipitate the onset of RA, although genetics still plays a part. Infections, smoking, and hormonal fluctuations are examples of potential triggers [46]. In RA, the immune system misinterprets synovium as a threat and mounts an offensive against it. When T- and B-lymphocytes are activated, pro-inflammatory cytokines like interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are released. Activation of synovial fibroblasts and the recruitment of immune cells are facilitated by pro-inflammatory cytokines. Synovial fibroblasts multiply and infiltrate the joint space, resulting in the development of a pannus, an atypical tissue that deteriorates bone and cartilage [47]. The pannus has a high degree of vascularization, which increases blood flow to the injured joint. Chronic inflammation and the degeneration of joint tissues are facilitated by angiogenesis, the formation of new blood vessels. Cartilage and Bone Destruction: The synovial tissue produces enzymes that aid in the breakdown of cartilage and bone, including matrix metalloproteinases (MMPs) [48]. Deformities and loss of function result from the destruction of joint structures. Systemic Effects: RA can affect organs such as the heart, lungs, and blood vessels in addition to its effects on the joints. People with RA may be more susceptible to cardiovascular disease as a result of chronic inflammation. Autoantibodies: People with RA frequently have rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies in their blood. The autoimmune response is facilitated by these autoantibodies [49].

With a better understanding of the pathophysiology of rheumatoid arthritis, targeted therapies that try to lower inflammation and modify the immune response have been developed. Certain medications, like biologic agents and disease-modifying antirheumatic drugs (DMARDs), target immune system components that

contribute to inflammation. In order to manage RA and avoid permanent joint damage, early diagnosis and intervention are essential [50].

Conclusion

RA is a crippling, inflammatory, chronic illness that can lead to long-term disability and joint damage. The avoidance of severe harm and the loss of vital physiological functions depends on early diagnosis and intervention. Treating physicians ought to think about following treat-to-target (T2T) guidelines, which state that goals should be outlined before protocols are put in place to accomplish and evaluate them. Better treatment results can also be ensured with an early referral to a specialist. Our understanding of disease mechanisms has improved due to developments in the field of molecular medicine, which can help in the development of more potent treatments. Both new and improved versions of existing treatment modalities have been created. The use of gene array analysis helps to identify the patients who will respond better to treatments. To find the best treatment for a given patient, this customization will enable faster treatment and reduce the chance that the disease will progress during the experimental phase. Additionally, gene array analysis is being used to identify patients who may be more susceptible to more severe forms of RA. It is anticipated that RA management techniques will see significant advancements.

Abbreviations

RA - Rheumatoid Arthritis; DMARDs - Disease-Modifying Antirheumatic Drugs**;** NSAIDs - Nonsteroidal Anti-Inflammatory Drugs**;** TNF - Tumor Necrosis Factor**;** IL – Interleukin**;** RF - Rheumatoid Factor**;** Anti-CCP - Anti-Cyclic Citrullinated Peptide**;** ESR - Erythrocyte Sedimentation Rate**;** CRP - C-Reactive Protein**;** MRI - Magnetic Resonance Imaging**;** ACR - American College of Rheumatology**;** MIAN - MTX-Induced Accelerated Nodulosis**;** COX – Cyclooxygenase**;** PPIs - Proton Pump Inhibitors**;** HLA - Human Leukocyte Antigen**;** MMPs - Matrix Metalloproteinases

Acknowledgements

I like to thank the authors for its contributions and whose work has been cited in this review, as their studies have significantly contributed to our understanding of rheumatoid arthritis. Finally, we extend our appreciation to our families for their unwavering support and encouragement during the preparation of this manuscript.

Competing Interest and Funding

This study was not funded.

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

No data was used for the research described in the article.

References

1) *Yanagisawa S, Nagasaki K, Chea C, Ando T, Ayuningtyas NF, Inubushi T, et al. (2022) Oral administration of bovine lactoferrin suppresses the progression of rheumatoid arthritis in an SKG mouse model. PLoS ONE 17(2): e0263254. DOI: https://doi.org/10.1371/journal.pone.0263254*
2) *Anjana Goel1, Sunanda Kulshrestha, et al. (2021) Review on Anti-Rheumatoid Arthritis Potential of Medicinal Plants International Journal of Current Research and Review Vol 13. Issue 03 DOI: http://dx.doi.org/10.31782/IJCRR.2021.13303*
3) *Turesson Wadell A, Ba¨rebring L, Hulander E, Gjertsson I, Hagberg L, Lindqvist HM, et al. (2021) Effects on health-related quality of life in the randomized, controlled crossover trial ADIRA (Antiinflammatory Diet In Rheumatoid Arthritis). PLoS ONE 16(10): e0258716.DOI: https://doi.org/10.1371/journal.pone.0258716*
4) *Lin Yen-Ju, Anzaghe Martina, et al.(2020) Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis Cells 2020, 9, 880; DOI: http://doi.org/10.3390/cells9040880*
5) *Chando Anita a, Momin Munira a,b,*, Quadros Mural a, Lalka Shaily et al.(2021) Topical nanocarriers for management of Rheumatoid Arthritis: A review Biomedicine & Pharmacotherapy 141 (2021) 111880. DOI: https://doi.org/10.1016/j.biopha.2021.111880*
6) *Paglia MDG, Silva MT, Lopes LC, Barberato-Filho S, Mazzei LG, Abe FC, et al. (2021)Use of corticoids and non-steroidal antiinflammatories in the treatment of rheumatoid arthritis: Systematic review and network metaanalysis. PLoS ONE 16(4): e0248866.DOI: https://doi.org/10.1371/journal.pone.0248866*
7) *Deyab G, Reine TM, Vuong TT, Jenssen T, Hjeltnes G, Agewall S, et al. (2021)Antirheumatic treatment is associated with reduced serum Syndecan-1 in Rheumatoid Arthritis. PLoS ONE 16(7): e0253247. DOI: https://doi.org/10.1371/journal.pone.025324*
8) *Kumar Janakiraman, Venkateshwaran Krishnaswami, Vijaya Rajendran, Subramanian Natesan, Ruckmani Kandasamy, et al. (2018) Novel nano therapeutic materials for the effective treatment of rheumatoid arthritis-recent insights. Materials Today Communications 17 (2018) 200–213. DOI: https://doi.org/10.1016/j.mtcomm.2018.09.011*
9) *Zhihao Zeng , Jiaoting Hu, Jieyi Jiang,Guanlin Xiao, Ruipei Yang, Sumei Li,Yangxue Li,Huajing Huang, Huixian Zhong, and Xiaoli Bi (2021) Network Pharmacology and Molecular Docking-Based Prediction of the Mechanism of Qianghuo Shengshi Decoction against Rheumatoid Arthritis. Hindawi, BioMed Research International Volume 2021, Article ID 6623912, 12 pages. DOI: https://doi.org/10.1155/2021/6623912*
10) *Gurleen Kour a,b, Syed Assim Haq c,d, Bijender Kumar Bajaj b, Prem N. Gupta c,d,*, Zabeer Ahmed et al.(2021) Phytochemical add-on therapy to DMARDs therapy in rheumatoid arthritis: In vitro and in vivo bases, clinical evidence and future trends. Pharmacological Research 169 (2021) 105618. DOI: https://doi.org/10.1016/j.phrs.2021.105618*

11) *Arzoo Pannu*, Ramesh K. Goyal*, Shreesh Ojha†, Mukesh Nandave et al. (2019) Naringenin: A Promising Flavonoid for Herbal Treatment of Rheumatoid Arthritis and Associated Inflammatory Disorders. Bioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases.*
DOI: https://doi.org/10.1016/B978-0-12-813820-5.00020-9

12) *Aditya S. Kulkarni*, Padmini S. Ghugre**, Shobha A. Udipi et al. (2016) APPLICATIONS OF NANOTECHNOLOGY IN NUTRITION: POTENTIAL AND SAFETY ISSUES . Novel Approaches of Nanotechnology in Food.*
DOI: http://dx.doi.org/10.1016/B978-0-12-804308-0.00015-7

13) *Jain, S.; Vaidya, A.; Gupta, P.K.; Rosenholm, J.M.; Bansal, K.K. et al. (2021) Antiarthritic Activities of Herbal Isolates: A Comprehensive Review. Coatings **2021**, 11, 1329.DOI: https://doi.org/10.3390/coatings11111329*

14) *Aletaha Daniel, Smolen Josef S.,et al.(2018) Diagnosis and Management of Rheumatoid Arthritis A Review, JAMA. 2018;320(13):1360-1372. DOI:10.1001/jama.2018.13103*

15) *Toussirot ´Eric, Michel Fabrice, Binda Delphine, Dumoulin Gilles, The role of leptin in the pathophysiology of rheumatoid arthritis, Life Sciences (2015), DOI: 10.1016/j.lfs.2015.05.001*

16) *Radu, A.-F.; Bungau, S.G. Management of Rheumatoid Arthritis: An Overview. Cells **2021**, 10, 2857. https://doi.org/10.3390/cells10112857*

17) *Lin Yen-Ju, Anzaghe Martina, et al.(2020) Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis Cells 2020, 9, 880; DOI: http://doi.org/10.3390/cells9040880*

18) *Derksen V. F. A. M., Huizinga T. W. J., Woude D. van der et al., (2017) The role of autoantibodies in the pathophysiology of rheumatoid arthritis; Semin Immunopathol (2017) 39:437–446 DOI: https://doi.org/10.1007/s00281-017-0627-z*

19) *Chando Anita , Momin Munira , Quadros Mural , Lalka Shaily et al. (2021) Topical nanocarriers for management of Rheumatoid Arthritis: A review. Biomedicine & Pharmacotherapy 141 (2021) 111880.*
DOI: https://doi.org/10.1016/j.biopha.2021.111880

20) *Huang J, Fu X, Chen X, Li Z, Huang Y , Liang C et al. (2021) Promising Therapeutic Targets for Treatment of Rheumatoid Arthritis. Front. Immunol. 12:686155.*
DOI: https://doi.org/10.3389/fimmu.2021.686155

21) *Benjamin Friedman , Bruce Cronstein et al.(2018) Methotrexate mechanism in treatment of rheumatoid arthritis. Joint Bone Spine xxx (2018) xxx–xxx.*
DOI: https://doi.org/10.1016/j.jbspin.2018.07.004

22) *Vijay Kumar, Jagat R. Kanwar, Anita Kamra Verma et al. (2020) Rheumatoid arthritis: basic pathophysiology and role of chitosan nanoparticles in therapy. Advances in the Development of Novel Carriers for Bioactives and Biological Agents. DOI: https://doi.org/10.1016/B978-0-12-819666-3.00016-X*

23) *Kumar Janakiraman, Venkateshwaran Krishnaswami, Vijaya Rajendran, Subramanian Natesan, Ruckmani Kandasamy (2018) Novel nano therapeutic materials for the effective treatment of rheumatoid arthritis-recent insights. Materials Today Communications 17 (2018) 200–213.*
DOI: https://doi.org/10.1016/j.mtcomm.2018.09.011

24) *Monika Joshi a , Kamla Pathak b , ∗ , Suneela Dhaneshwar et al.(2022) Nanotechnology-based strategies for effective delivery of phytoconstituents for the management of rheumatoid arthritis. Pharmacological Research - Modern Chinese Medicine 2 (2022) 100061.DOI: https://doi.org/10.1016/j.prmcm.2022.100061*

25) *Aisha Mobashar,Arham Shabbir , Muhammad Shahzad,Saeed-ul-Hassan et al. (2020) Evaluation of Immunomodulatory and Antiarthritic Potential of Trigonella gharuensis Extracts. Hindawi,Evidence-Based Complementary and Alternative Medicine Volume 2020, Article ID 8836080, 7 pages.DOI: https://doi.org/10.1155/2020/8836080*

26) *Jurca, T.; Józsa, L.; Suciu, R.; Pallag, A.; Marian, E.; Bácskay, I.; Mures, an, M.; Stan, R.L.; Cevei, M.; Cioarˇa, F.; Vicas, , L.; et al. (2021) Formulation of Topical Dosage Forms Containing Synthetic andNaturalAnti-Inflammatory Agents for the Treatment of Rheumatoid Arthritis. Molecules **2021**, 26, 24. DOI: https://dx.doi.org/10.3390/molecules26010024*

27) *Janakiraman K, Krishnaswami V, Rajendran V, Natesan S, Kandasamy R, Novel Nano therapeutic materials for the effective treatment of Rheumatoid Arthritis- recent insights, Materials Today Communications (2018). DOI: https://doi.org/10.1016/j.mtcomm.2018.09.011*

28) *Shimaila eram, Md. mujahid*, Paramdeep bagga, Muhammad arif, et al., (2019) A REVIEW ON PHYTOPHARMACOLOGICAL ACTIVITY OF ALPINIA GALANGA Int J Pharm Pharm Sci, Vol 11, Issue 3, 6-11. DOI: http://dx.doi.org/10.22159/ijpps.2019v11i3.31352*

29) *Sarkar, K.K., Mitra, T., Acharyya, R.N. et al. Phytochemical screening and evaluation of the pharmacological activities of ethanolic extract of Argemone mexicana Linn. aerial parts. Orient Pharm Exp Med **19**, 91–106 (2019). https://doi.org/10.1007/s13596-018-0357-3*

30) *Shaikh, S., Dubey, R., Dhande, S., Joshi, Y. M., & Kadam, V. J. (2012). Phytochemical and pharmacological profile of Aphanamixis polystachya: an overview. Research Journal of Pharmacy and Technology, 5(10), 1260-1263.*

31) *Daoudi Amine, Bammou Mohamed, Ibijbijen Jamal, Nassiri Laila et al.,(2017).Antibacterial Activity of Aqueous Extracts of Anacyclus Pyrethrum (L) Link and Corrigiola Telephiifolia Pourr. From the Middle Atlas Region-Morocco. European Scientific Journal November 2017 edition Vol.13, No.33. Doi: http://doi.org/10.19044/esj.2017.v13n33p116*

32) *Rahman, H., Eswaraiah, M. C., & Dutta, A. M. (2016). Anti-arthritic activity of leaves and oil of Aquilaria agallocha. Haya: The Saudi Journal of Life Sciences, 1(1), 34-43.*

33) *Shivamanjunath, M. P., & Sreenath, K. P. (2013). Phytochemical studies on Cardiospermum canescens Wall. American International Journal of Research in Formal, Applied and Natural Sciences, 3, 61-65.*

34) *Vinod Nair, Surender Singh, Yogendra Kumar Gupta et al., (2012) Anti-granuloma activity of Coriandrum sativum in experimental models. Journal of Ayurveda & Integrative Medicine , January-March 2013 , Vol 4 , Issue 1.DOI: http://doi.org/10.4103/0975-9476.109544.*

35) *John K. Triantafi llidisa, Aikaterini Triantafyllidia, Constantinos Vagianosb, Apostolos Papalois et al., (2016) Favorable results from the use of herbal and plant products in*

inflammatory bowel disease: evidence from experimental animal studies. Annals of Gastroenterology (2016) 29, 268-281. DOI: http://dx.doi.org/10.20524/aog.2016.0059

36) *Lee D, Kim SJ, Kim H.et al., (2020). A 12 week, randomized, doubleblind, placebo-controlled clinical trial for the evaluation of the efficacy and safety of HT083 on mild osteoarthritis. Medicine 2020;99:28(e20907). DOI: http://dx.doi.org/10.1097/MD.0000000000020907*

37) *Mohammed Rahmatullah, Rownak Jahan, A.K. Azad, Syeda Seraj, Md. Mahbubur Rahman, Anita Rani Chowdhury, Rahima Begum, Dilruba Nasrin, Zubaida Khatun, Mohammad Shahadat Hossain, Mst. Afsana Khatun, Z.U.M. Emdadullah Miajee et al., (2010). A Randomized Survey of Medicinal Plants used by Folk Medicinal Practitioners in Six Districts of Bangladesh to Treat Rheumatoid arthritis. Adv. in Nat. Appl. Sci., 4(2): 124-127, 2010.*

38) *Mali PY, Panchal SS, Euphorbia neriifolia L. et al.,(2017): Review on botany, ethnomedicinal uses, phytochemistry and biological activities, Asian Pacific Journal of Tropical Medicine (2017), doi: http://doi.org/10.1016/j.apjtm.2017.05.003.*

39) *Rathod, V. D., Digambar, N. W., Pillai, S., Bhangale, J. O., & Bhangale, P. J. (2018). Antiarthritic activity of ethanolic extract of Ficus religiosa leaves in FCA induced arthritis in rats. World J. Pharm. Res, 7(2), 778-78.*

40) *Kanwaljeet Singh, Pankaj Kumar, BushanKumar, Javaid Fayaz Lone, P.R. Sharma and Sumeet Gairola et al., (2020) MORPHO-ANATOMICAL AND PALYNOLOGICAL STANDARDIZATION AND DNA BARCODING OF FRITILLARIA CIRRHOSA D. DON (SYN. FRITILLARIA ROYLEI HOOK.). Plant Archives Vol. 20, Supplement 2, 2020 pp. 1304-1313.*

41) *Labony Khandokar , Md. Sazzadul Bari , Veronique Seidel , Md. Areeful Haque et al.,(2021). Ethnomedicinal uses, phytochemistry, pharmacological activities and toxicological profile of Glycosmis pentaphylla (Retz.) DC.: A review. Journal of Ethnopharmacology 278 (2021) 114313. DOI:https://doi.org/10.1016/j.jep.2021.114313*

42) *Al-Snafi, A. E. (2018). Therapeutic importance of Hyoscyamus species grown in Iraq (Hyoscyamus albus, Hyoscyamus niger and Hyoscyamus reticulates)-A review. IOSR Journal of Pharmacy, 8(6), 18-32.*

43) *Srivastava, D., & Shukla, K. (2015). Ipomoea cairica: a medicinal weed with promising health benefits. International Journal of Information Research and Review, 2(5), 687-694.*

44) *Rachid Ait Babahmada, Abdellah Aghrazb, Aziz Boutafdaa, Eleni G. Papazoglouc, Petros A. Tarantilisd, Charalampos Kanakisd, Mohamed Hafidia, Yedir Ouhdouche, Abdelkader Outzourhitf, Ahmed Ouhammou et al., (2018). Chemical composition of essential oil of Jatropha curcas L. leaves and its antioxidant and antimicrobial activities. Industrial Crops & Products 121 (2018) 405–410.DOI: https://doi.org/10.1016/j.indcrop.2018.05.030*

45) *Parvathy Velayudhan Nair, Bindulatha Nair et al., (2017) Muscle relaxant activity of hydroalcoholic extract of Mimosa pudica whole plant in mice. National Journal of Physiology, Pharmacy and Pharmacology , Vol 7 , Issue 4. DOI: https://doi.org/10.5455/njppp.2017.7.1235704012017*

46) *Jacqueline Bullock, Syed A.A. Rizvi, Ayman M. Saleh, Sultan S. Ahmed, Duc P. Do,[e] Rais A. Ansari, Jasmin Ahmed (2019)Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract. 2019 Mar; 27(6): 501–507. DOI: https://doi.org/10.1159/000493390*

47) *Singh, D., Vaghela, J. S., & Kumar, A. (2022). Comparative evaluation of anti-arthritic activity of Pongamia pinnata, Bryophyllum pinnata and their combined formulation in Fca induced arthritis rat model. Journal of Pharmaceutical Negative Results, 1565-1571.*

48) *Hu J, Zhao L, Li N, Yang Y, Qu T, Ren H, et al. (2022) Investigation of the active ingredients and pharmacological mechanisms of Porana sinensis Hemsl. Against rheumatoid arthritis using network pharmacology and experimental validation. PLoS ONE 17(3): e0264786. DOI: https://doi.org/10.1371/journal.pone.0264786*

49) *Senthamil Selvan Perumal, Sanmuga Priya Ekambaram & T. Dhanam (2017) Invivo antiarthritic activity of the ethanol extracts of stem bark and seeds of Calophyllum inophyllum in Freund's complete adjuvant induced arthritis, Pharmaceutical Biology, 55:1,1330-1336, DOI: https://doi.org/10.1080/13880209.2016.1226346*

50) *Vetriselvan Subramaniyan, et al., (2019) Hemidesmus indicus and Usage for Arthritic Conditions. Bioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases. DOI: https://doi.org/10.1016/B978-0-12-813820-5.00029-5*