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RHEUMATOID ARTHRITIS: AN UPDATE ON DIAGNOSTIC MODALITIES AND TREATMENT PROTOCOLS

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ABSTRACT: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that permanently damages and disables the joints if left untreated. Much research is being carried out; however, any detailed information that could impart knowledge of all the major aspects in an undivided form is still lacking. This review attempts to revive the existing knowledge on RA and provides comprehensive data and current information about the classification criteria for the diagnosis of rheumatoid arthritis and treatment protocol for the management of Rheumatoid arthritis. Early and accurate diagnosis is essential as it can slow down the progression of the disease, permanent joint damage and disability in up to 90% of RA patients. This article also focuses on various diagnostic modalities which help in the diagnosis of RA, and synthetic medicines available for the cure of RA. It provides a section about non-pharmacological and herbal treatment options available for the management of Rheumatoid arthritis.

INTRODUCTION: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease (the immune system mistakenly attacks the healthy tissues in joints) of unknown origin with a worldwide prevalence of 0.5-1% among adults. If not treated, RA predominately affects the joints and characterized by synovitis, systemic inflammation (triggered by metabolites of arachidonic acid and several inflammatory cytokinin's), and auto antibodies that can permanently damage and disables the joints [1, 2]. RA can strike at any age and more frequently occurs in persons between the ages of 30-50 years.

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Moreover, women are more likely to develop RA as compared to men, *i.e.*, approximately 4:1 [3]. Exact etiology of RA is unknown, but it could be multifactorial [4]. It can arise due to genetic, epigenetic, and environmental factors such as smoking cigarettes, dust exposure, and especially microbiome [5]. Environmental (*i.e.*, smoking, obesity, infections caused by microorganisms) as well as genetic factors *i.e.*, epigenetic modification, alteration of T and B cell functions, cytokinin production, and activation of immune cells) induces occurrence of RA.

Likewise, synovial injury and hyperplasia of synovial fibroblast lead to RA by generating inflammatory conditions [6]. Rheumatoid arthritis is associated with decreased life expectancy and quality of life; thus, its early diagnosis and immediate and effective treatment is crucial to prevent the joints from deterioration and adverse disease outcomes. The goal of RA treatment is to

lessen the inflammation and pain in joints, enhance joint function, and prevent the joints from destruction and deformity [7]. There are several approaches for the management of RA that include uses of synthetic and herbal drugs.

This review emphasizes the recent updates on diagnostic tools and treatment protocols for RA. Various marketed drugs and their mechanism of action are also mentioned in this review.

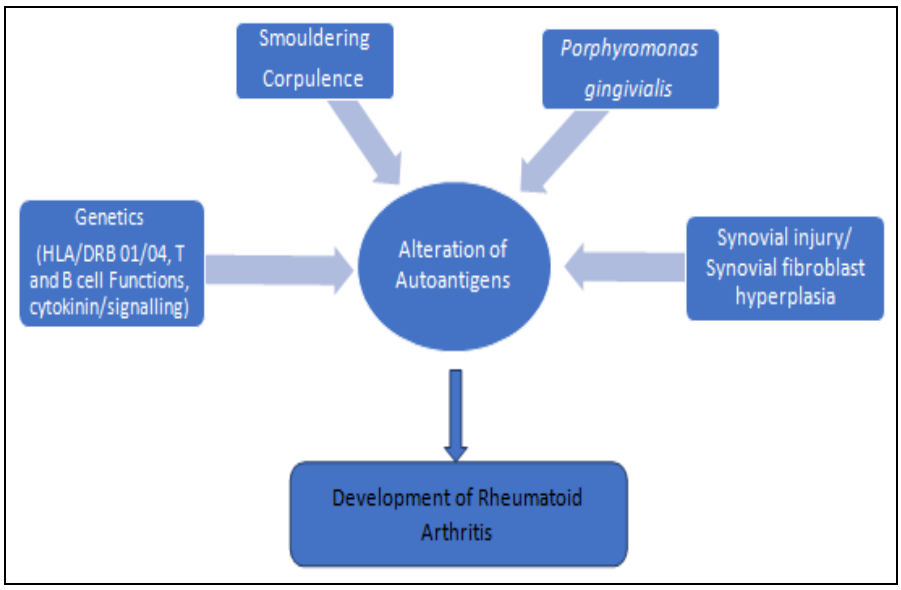

FIG. 1: FACTORS CONTRIBUTING TO THE DEVELOPMENT OF RHEUMATOID ARTHRITIS

Clinical Presentation: Clinical presentation can vary in individuals suffering from RA but most commonly, pain with edema and stiffness in several joints (most typically in the wrists, proximal interphalangeal and metacarpophalangeal joints) as well as possibly cartilage and bone degradation can be involved, which results in the loss of joint functions [8]. Morning stiffness in or around the joints, lasting at least 1 hour before maximal improvement, is the characteristic sign of rheumatoid arthritis and follows circadian rhythm of proinflammatory cytokines and IL-6 [9]. On examination of the joints, swelling or subtle synovial thickening may also be visible due to synovitis Boggy. Along with physical signs and symptoms, abnormality in various laboratory markers like Interleukins-6 (IL-6), C - reactive protein (CRP), and citrullinated protein antibodies (ACPA) can also be seen [10]. Extraarticular signs also occur in RA patients which can involve Cardiovascular, pulmonary, nervous, and reticuloendothelial systems and can cause vasculitis, hematologic abnormalities, Flety's syndrome, and visceral involvement [11].

Diagnostic Investigations: Unfortunately, there are no consensus criteria for the diagnosis of RA, but it is essential to diagnose the RA for early commencement of the treatment, as early diagnosis can capture the disease and thus can slow down the progression of the disease, permanent joint damage, and disability in up to 90% of the RA patients. Clinically, RA starts with the swelling and pain around the joints, morning joint stiffness, and abnormal laboratory results but intolerable flank pain and swelling of the joints are not confirmatory indications of RA only. So for the diagnosis of RA, Patient symptoms, Physical examination findings, family history, valuation of risk factors, assessment of joints by ultrasound and MRI imaging, and Quantitation of the laboratory markers such as increased CRP and Erythrocyte sedimentation rate (ESR) level in serum and detection of RA specific autoimmune antibodies should be estimated and based on the combined results of above tests RA can be confirmed [6, 12].

Criteria to Classify Rheumatoid Arthritis (2010 American College of Rheumatology) [13, 14]: As there is no perfect diagnostic marker for the diagnosis of RA, so, the American College of Rheumatology (ACR) suggested the classification criteria for the correct diagnosis of the disorder. The requirements are recommended for the classification of newly presenting patients of RA.

TABLE 1: CLASSIFICATION CRITERIA FOR RA AS PER AMERICAN COLLEGE OF RHEUMATOLOGY 2010

Target population, should be tested who: Have a minimum, one joint with clinical synovitis (swelling). With synovitis which cannot be explained or diagnosed as another disease	Score
Classification criteria for rheumatoid arthritis (score-based algorithm): Score from categories A-D should be combined, if the total score is more than or equal to 6/10 than the patient is diagnosed with RA however if the total score is less than or equal to 6/10 the patient is not diagnosed with RA, but the status of the patient should be reassessed over a period of time	
Joint Involvement	
>10 joints along with involvement of at least one small joint	5
4-10 small joints (with or without involvement of large joints)	3
1-3 small joints (with or without the involvement of large joints)	2
2-10 large joints	1
1 large joint	0
Serology (At leastone of the test results is needed for the classification)	
High positive RF or High positive ACPA	3
Low positive RF or Low positive ACPA	2
Negative RF and Negative ACPA	0
Acute phase reactants (At minimum one of the test results is needed for the classification)	1
Abnormal CRP and ESR	0
Normal CRP and ESR	
Duration of symptoms	
Greater than or equal to 6 weeks	1
Less than 6 weeks	0
	∑= Overall Score

RF: Rheumatoid Factor, CRP: C - reactive protein, ACPA: Citrullinated protein antibodies, ESR: Erythrocyte sedimentation rate.

Joint involvement refers to any swollen or tender joints found on examination, which can be confirmed for synovitis with imaging. The assessment excludes the distal interphalangeal joints, first carp metacarpal joints and first metatarsophalangeal joints.

Large Joints: such as shoulder, elbow, hips, knee and ankle. Small joints refer to metacarpophalangeal joints, proximal inter-phalangeal joints, 2nd through 5th meta-tarsophalangeal joints, thumb interphalangeal joints and wrist. Negative refers to IU values ≤ ULN for laboratory and assay; low positive refers to IU value > ULN but ≤ 3 times ULN for laboratory and assay; high positive value refers to > 3 times the ULN for laboratory and assay [13, 14].

Diagnostic Modalities:

Serological Analysis: Serological diagnostic testing is very important for the timely detection of RA. Any excess of autoantibodies and proteins can be related to RA and its numerous manifestations. But for clinical practice, immunoglobulin (Ig) M, rheumatoid factor (RF), and its citrullinated protein antibodies (ACPA), along with the predominance of IgG anti-cyclic citrullinated peptides (anti-CCPs) are considered across the world [15].

Rheumatoid Factor: RF is the first immunologic marker, and its increased level is detected in 80-85% of patient's serum, suffering from the RA [16]. RF consists of auto-reactive immunoglobulins which are focused on Fc region of IgG.

Clinically IgM RF comprises the major RF species in the patient with RA. But, the increased level of the RF is not specific to the presence of RA only as the level of RF can also increase in the people suffering from other diseases like Hepatitis C. Various tests methods are used to detect RF, but ELISA and Nephelometry are the standard methods which are used to determine RF levels in the serum However sensitivity of the test is 70-80% [17]. Nishimura also proved in the meta-analytical review that the anti-CCP antibodies are more specific than RF [18].

Anti-citrullinated Protein Antibodies (ACPA): It was an important discovery for the characterization of autoantigens containing the aminoacid citrulline in patients of RA.ACPA appears in 2/3rd of all the RA patients [19]. ACPA autoantibodies target several proteins containing citrulline epitopes which is a consequence of the deamination of arginine in RA patients.

In 1964 first protein auto antigen, antiperinuclear factor was identified by RA-specific autoantibody on buccal epithelial cells by an indirect immunofluorescence method.

In succeeding years, further autoantibodies were identified like anti-keratin antibodies, anti-vimentin, and antifilaggrin. Later, it was understood that these target specificities were critically reliant on posttranslational modifications (Citrullination), which alters the charge and thus the protein's 3-D structure, which causes changes in the antigenic properties [15, 20]. ACPA can be detected in the serum of RA patients up to 14 years before the appearance of the first symptom of the disease in the patient. Thus it is proved to be a very important diagnostic tool for the early detection of RA [20].

Clinical Biomarkers: C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) are two important clinical biomarkers used for diagnosing RA and indicating RA patient's inflammatory condition. According to 28 joint Disease Activity Score (DSA-28), elevated CRP level is related to increased RA disease activity, and thus CRP level is used to monitor systemic inflammation and clinical outcome [21]. CRP level is also related to radiological damage in RA.

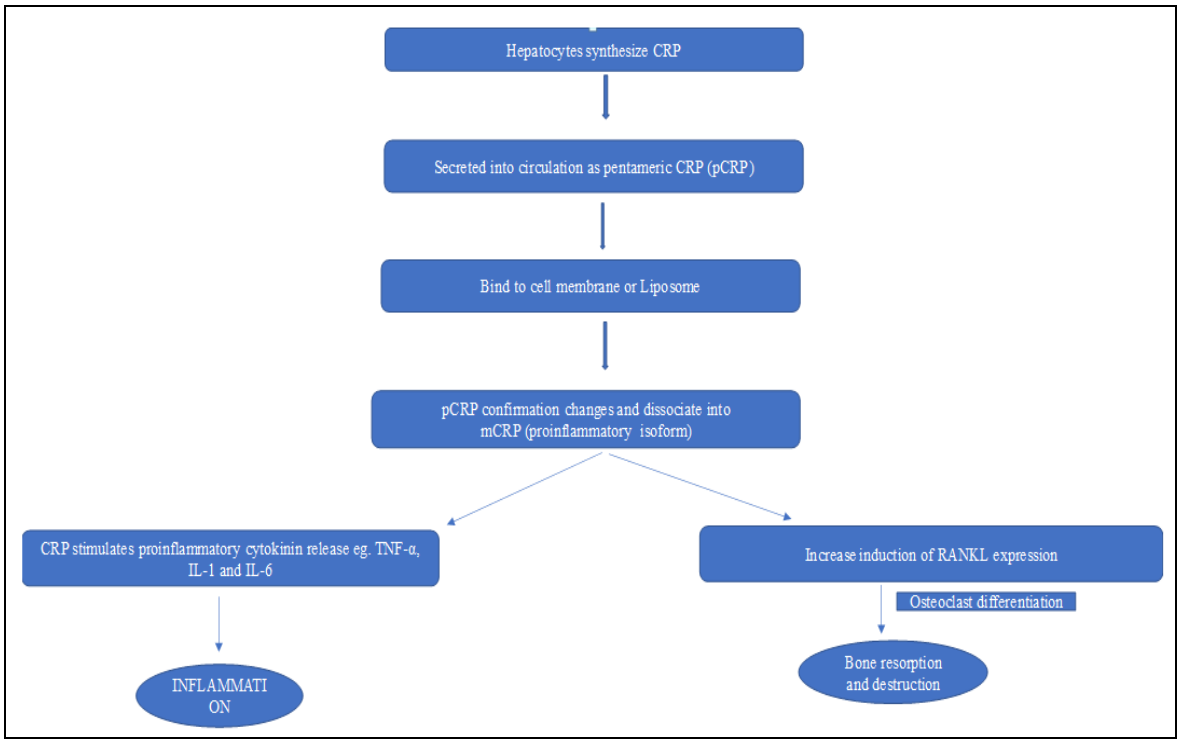

FIG. 2: ROLE OF C- REACTIVE PROTEIN IN INFLAMMATION

As CRP level is correlated with histological changes in the synovium, disease activity, clinical symptoms and inflammation, it is a vital marker for diagnosing and monitoring RA in patients.ESR is also a serum diagnostic test and its level generally increases in the state of inflammation, infection, and autoimmune disorders [22].

Imaging: Imaging is the most important diagnostic modality which provides ample information regarding the disease activity.

Anatomical Imaging Modality: Radiography is one of the preliminary most common and cost-effective imaging modalities for detection and follow-up study in patients with RA. It helps in visualizing joint destruction, which occurs in RA, but the sensitivity of radiography is low for soft-tissue edema, bone marrow changes, and synovial thickening at early stage of the disease. Also, it may not help detect bone erosion, which usually occurs at the early stage of the RA. So, with radiography modality, RA can be detected at the advanced stage only and it could not reflect any problem at the early stage of RA [23].

Ultrasound and Magnetic Resonance Imaging: Ultrasound (US) and Magnetic Resonance Imaging

(MRI) can be utilized to diagnose the RA at an early stage and can be used to monitor the RA patients. Both the tools provide enough information regarding the stage or phase of RA, which further helps to determine the treatment that should be recommended to the patients. Bone erosion is a distinctive characteristic of RA and appears after 6-8 weeks of the onset of the symptoms and can be detected with the help of MRI and ultrasound [24].

US technique includes the use of grayscale imaging and doppler modalities. With these improved technologies, anatomic structures can be imaged through a gray scale, while Doppler can detect blood flow. US help sin detecting and semi-quantitatively assess tendon, joint inflammation, and damage. It allows visualizing morphological and structural changes in the joints and tendons, which is induced by synovitis (detecting synovial stratum thickening of inflamed joints as well as tendon sheath of the greyscale) and can also help to detect fluids in joints, bursae and tendon sheath and thus serve as a brilliant diagnostic tool which can be used to assess the integrity of the tendons and ligaments as well as imaging enthesitis [25, 26].

Musculoskeletal US modality helps monitor the RA patient's response to the treatment and guides intra-articular procedures. Using the musculoskeletal US, patients on RA treatment with different medications (especially biological treatment) can also be monitored. As US does not involve any ionization radiation so, it can also be used to assess juvenile RA [27].

On the other hand, MRI is more sensitive and specific than US and can assess or visualize every single structure that could be intricate in the disease, like a synovial membrane, cartilage, ligaments, bones, intra and extraarticular fluid collection, tendons, and sheath of tendons. MRI can be applied to ascertain the occurrence of rheumatoid arthritis, but its use is limited due to cost factors [28]. 54-64% of joints inflammation without swelling can be detected by the MRI modality [29].

Computed Tomography (CT): The role of CT in the early detection of RA is very limited as this technique involves the use of ionizing radiation, and its sensitivity for the soft tissues is also limited [30].

Molecular Imaging Modality: Molecular imaging is a crucial modality that plays a significant role in early and reliable detection of the disease, as cellular and molecular changes often occur long before the appearance of the anatomical or metabolic changes [31]. It aims to visualize, characterize and quantify molecular and cellular processes in living organisms using remote imaging detectors. This novel tool plays a vibrant role in visualizing the early functional changes and the extent of disease in RA. This non-invasive technique helps evaluate pathological and physiological processes, assists in the early diagnosis of RA, facilitates disease monitoring, helps in the selection of treatment, and enables the prediction of the possible outcome of the selected treatment [32]. It is a very beneficial tool as, without any surgical intervention or biopsies, it could determine the pathology of the diseased tissues, and personalized treatment can also be planned for the patients [33].

Optical Imaging Modalities: Optical imaging is a promising non-invasive, quick, simple, and non-ionizing technique that uses visible or nearly visible light as a primary imaging method. Optical imaging techniques encompass bioluminescence and fluorescence. Bioluminescence enables in vivo visualization of biological processes, but its clinical use is limited, while fluorescence imaging is more promising for clinical use [38]. Near infra-red fluorescence, optical imaging with non-specific dyes is another novel tool that can detect and monitor arthritides and takes less time as compared to US and MRI [34].

Thermography: Thermography is a non-invasive scanning method that eliminates the need for physical contact between the measuring device and the scanned object. This technique depends on the principle that Arthritic joints tend to be warmer as compared to the normal joints. As skin can efficiently dissipate heat to the surrounding, Clinical IR thermography measures joint heat and help to perceive, record, and generate color images of patient's skin's apparent temperature. Variation of skin temperature can also be assessed qualitatively and quantitatively with modern thermal imagers like liquid crystal or electronic infrared telethermographer [35, 36]. Tan Y Klooks for the scope of thermography as a potential tool for

detecting the joint inflammation in RA in comparison to ultrasonography and the outcome of the study suggests that the patients found positive for joint inflammation viaultra sound detected method have significantly higher temperature readings, however in identifying the difference in swollen tender, swollen on-tender and non-swollen tender joints the results of thermography were not significant in comparison to ultrasonography [37].

Near-Infrared Imaging Modality (NIR Imaging): Interest has developed in this technique as it helps in the early diagnosis of RA. It is a technique that detects the changes in the scattering of the light transmitted by the joints [38]. In this technique, NIR light propagation helps in recording signals after penetrating 1 cm through tissues and human peripheral joints. On the other side, with optical to mographic reconstruction, intravenously administered NIR fluorochromes can be localized and quantified after up to 10 cm of tissue penetration. Still, healthy and inflamed joints cannot be differentiated based on changes in light scattering due to limited resolution, but optical tomography, when combined with NIR imaging, assists to differentiate healthy and inflamed joints in the patients more precisely [39]. This technique is highly sensitive and can rapidly generate images, so it is very useful to study the pharmacokinetics and biodistribution of nano-medicines by following the fluorescent signals [40].

Nuclear Imaging: Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPCET). Nuclear medicine imaging is based on detecting gamma rays emitted by radiopharmaceuticals consisting of biologically active molecules coupled with unstable radioisotopes [41]. In this technique, the radiopharmaceutical is injected into the patient's body, and then gamma radiation emission within the body is detected with the help of an external detector or camera. Planar scintigraphy captures 2D images, while newer techniques like PET and SPCET, which are more sensitive than structural imaging, produce 3-dimensional (topographic) images. PET and SPCET can be differentiated based on the type of radiotracer used. For example, 99mTc is used for SPCET, while 18F-FDG (18 F fluorodeoxyglucose), a positron emitter, is used in PET to study inflamed synovial joints. This technique helps assess the severity of the disease, facilitates early diagnosis, monitors therapeutic effects, and complements the data obtained from structural imaging techniques [42]. As a single tool, its clinical use is limited due to its poor spatial resolution and insufficient anatomical evidence, but for its beneficial effects, nuclear imaging modality can be coupled with other conventional modalities like Computed tomography (CT) and MRI [43].

Treatment Protocols: Medical intervention comes into play once Rheumatoid arthritis is confirmed as per ACR guidelines. Unfortunately, there is no cure for RA, and drugs can be given only to manage the disease; thus, the treatment of rheumatoid arthritis is very intricate and depends on the patient's treatment goal, disease activity, severity, and patient compliance and comorbidities. Physician's decision to choose treatment can include treatment with i) Non-steroidal anti-inflammatory agents (NSAIDS) ii) glucocorticoids iii) DMARDs and iv) Physical therapy depending on the above-said parameters [44, 45]. To support high-quality clinical care and facilitate physician's and patient's, ACR recommended the guidelines that serve as a tool for the treatment or management of RA; however, treatment's decision should be made based on the patient's goals, values, preferences, and comorbidities.

Non-steroidal Anti-inflammatory Drugs (NSAID): NSAIDs are the common drugs like Aspirin, sulindac, Etodolac, etc., which can be given to the patients for the symptomatic relief of RA. These drugs relieve pain, reduce swelling, and improve joint functions, but they do not affect RA disease activity. These drugs can neither prevent disease progression nor do they affect joint damage [46]. NSAIDs act by inhibiting cyclooxygenase (COX) enzymes responsible for producing proinflammatory prostaglandins [47]. NSAIDs provide symptomatic respite but are accompanied by gastrointestinal, cardiovascular, hepatic, and renal side effects [48]. Disease-modifying antirheumatic drugs (DMARDs) in Rheumatoid arthritis. A wide range of drugs can be used in RA, but DMARDs are the first choice of drugs used in RA. DMARDs are immunosuppressive or immunomodulatory agents that slow the progression of joint damage and reduce the immune response that contributes to pain and

inflammation. DMARD scans are categorized as conventional synthetic disease-modifying antirheumatic drugs (cs DMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (ts DMARDs) [49].

Conventional Synthetic DMARDs (cs DMARDs): Cs DMARDs are indicated as first-line treatment for RA, either alone or in conjunction with other anti-inflammatory medications. Cs DMARDs can relieve the symptoms and delay the progression of the disease. Commonly used conventional DMARD's include methotrexate (most commonly used as cost-effective, provides long-term efficacy, and acceptable safety profile), hydroxychloroquine, sulphasalazine, and leflunomide [50]. However, methotrexate (MTX) is the most commonly used cs DMARDs, but it is less likely to be prescribed to pregnant women as it is associated with congenital malformations [51].

Biologic DMARDs: Biologic DMARDs (bDMARDs) are recombinant biologic molecules that recognize and target high specificity extracellular inflammatory mediators. b DMARD includes TNF inhibitors, T-cell costimulatory inhibitors, Interleukin(IL)-1 receptor inhibitors, IL-6 receptor inhibitors, and Anti-CD20 antibodies, among which TNF inhibitors are the most widely used biological therapy [52]. Biologic DMARDs increase the effectiveness of the treatment and provide better clinical outcomes compared to cs DMARDs [53].

TNF Inhibitors: TNFα is homotrimer protein consisting of 157 amino acids generated by the macrophages activated by inflammatory cytokines produced by T cells and causes inflammation and joint destruction. This TNFα can bind to TNFR1 or TNFR2 receptor, majorly in autoimmune disorder TNF αbinds to TNFR1 and initiate an inflammatory response. The TNF inhibitors block the action of TNF α on both these receptors, thus relieving the RA patient and increasing the quality of life of RA patients [54]. Currently, 5 clinically approved available TNF inhibitors are infliximab (is chimeric antibody, given intravenously in every 8 weeks), adalimumab (is a human monoclonal antibody given subcutaneously every 2 weeks), certolizumab pegol (injected subcutaneously in 2 -4 weeks), golimumab (is a human monoclonal antibody to TNF can be given subcutaneously every 4 weeks or intravenously every 8 weeks) and etanercept (is TNF receptor fusion protein is given subcutaneously every week) [55].

TNF inhibitors are expensive as well as increases the burden of RA patient but Said Cynthia in his research, has revealed that in the short term of 6 months, the patient's quality of life increases and so, the pharmacoeconomic impact also increases eventually [56]. Prior to start with TNF inhibitors, therapy patient should be screened for latent tuberculosis and other preexisting infections. After screening anti- tuberculosis prophylaxis should be considered for high-risk patients. TNF inhibitors should be avoided for patients suffering from chronic infections like Hepatitis B. Live vaccination is also contraindicated during TNF inhibitors therapy. Treatment with TNF inhibitors should be stopped in case of adverse effects, inefficacy, pregnancy, or other serious infections [57, 58].

T-cell Costimulatory Inhibitors: Abatacept activated T cells are associated with RA's pathogenesis. These activated cells cause magnification of the inflammatory cascade and result in inflammation and destruction of joints in RA [59]. Abatacept which is a genetically engineered soluble fusion protein, inhibits T-cell activation by binding with CD80/86 receptors on antigen-presenting cells and modulating its interaction with CD28 (a signal required for full activation of T cells) and thus results in inhibition of T cell proliferation and B cell stimulation which causes a decrease in the serum level of biomarkers [60]. Schiff M put his 7 years of research and written a Meta analytical review and demonstrated that abatacept is a clinically meaningful, effective, and persistent treatment option with an established safety profile for the patients suffering from RA and in moderate to severe disease activity state with inadequate response to MTX/DMARDs or TNF inhibitors. He suggested that abatacept, when given at a very early stage of the disease, can alter the progression of the disease [61]. Earnest Choy also confirmed in his meta-analytical review that abatacept is clinically beneficial in terms of treatment persistence, durability, and risk-benefit profile [62].

IL-1 Receptor Inhibitors: Example: Anakinra.

IL-1 is a proinflammatory cytokine responsible for the destruction of joints by activating osteoclasts, stimulating matrix metalloproteinase production and impairing cartilage recovery [63]. IL-1 receptor inhibitors are natural inhibitors of IL-1.Anakinra is a recombinant form of human IL-1 receptor antagonist that acts by specifically modifying the immune response of IL-1. Anakinra slows down the progression of structural joint degeneration in RA patients and helps to preserve and protect bone and cartilage [64]. It can be given daily as a subcutaneous injection [65]. Anakinra can cause reaction at the site of injection, infections at higher doses and immunogenicity as adverse effects and it is also less effective than TNF inhibitors [67, 68].

IL-6 Receptor Inhibitors: Example: tocilizumab and sarilumab.

IL-6 is a proinflammatory cytokine that exerts pleiotropic activity by activating glycoprotein gp130 via binding to IL-6 receptors. IL-6 receptor is composed of membrane-associated IL-6R-α (mIL6R) and its soluble form (sIL-6R). IL-6 binds to transmembrane IL-6 receptors (mIL-6R) to form a complex that further induces homodimerization of gp 130 and activates the signaling system via Janus kinase in target cells and is known as classic or classic cis signaling. IL-6R exists in soluble form(sIL-6R), which deficits transmembrane and cytoplasmic components. sIL-6R also has a similar affinity for IL-6. The complex of sIL-6R and IL-6 can also activate gp 130, known as trans-signaling [68, 69].

In the RA patients, the level of IL-6 increases in the serum as well as in synovial fluids and is responsible for inflammation, joint destruction and osteoporosis. IL-6 destructs the joints by inducing endothelial cells, which generates IL-8 and Monocyte chemo attractant protein-1 and induces proliferation of synoviocytes and differentiation of osteoclast *via* RANKL expression associated with RA. IL-6 inhibitors prevent the binding of IL-6 with IL-6 receptors and lead to clinical and biochemical improvement [70, 71]. Tocilizumab (TCZ) was the first recombinant humanized antiIL-6R monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor, inhibits dimerization of gp130, which decreases proinflammatory effects of IL-6 and increases the expression of genes correlated with healing in synovial fluids [72, 73]. Tocilizumab is available in Intravenous and subcutaneous formulations. Tocilizumab in monotherapy or in combination therapy provides quick and continuous improvement in clinical, biochemical, and radiographic outcomes in early as well as in established RA. Tocilizumab has many benefits over other anti-rheumatoid arthritic medicines. TCZ has greater clinical effectiveness than MTX, has broad therapeutic application, and can also ameliorate amyloidosis by normalizing amyloid A levels in the serum of RA patient [74].

But as it is an expensive drug, it is mostly prescribed to the patients with the worst disease activity, and its continuation also depends on the adequate outcome. It has long-term efficacy and has good safety profile. Tocilizumab is contraindicated only in the case of TCZ hypersensitivity [75].

Sarilumab: It is a human IgG1 anti-IL-6R monoclonal antibody that specifically binds to soluble and membrane-bound IL-6R and blocks IL-6 mediated cis as well as trans-signaling pathways. It is administered subcutaneously in every 2 weeks and is recommended for the adults with moderate to severe RA who responded inadequately to at least one DMARD. Compared to TCZ, sarilumab binds to IL-6R with higher affinity and inhibits IL-6 induced cell proliferation at lower concentrations with a longer half-life. Sarilumab improves signs and symptoms of RA, and the physical function of the RA patients and decreases the progression of structural damage (indicated by erosion score, joint space narrowing [76, 77]. Its safety profile is also consistent with TCZ [78].

Anti-CD20 Antibody: Rituximab was the first genetically engineered chimeric monoclonal antibody that targets CD20 antigen on the B cells (responsible for inflammation cascade) and is currently used to treat RA. Rituximab lowers the local Th17 response in RA patients, resulting in reduced inflammation and better clinical outcome [79, 80].

Rituximab has long-term effects and is well tolerated with no serious adverse effects [81, 82]. ts DMARD'sacts by inhibiting Janus kinase enzymes, including tofacitinib, baricitinib, and upadacitinib.

To facitinib was the first targeted clinically approved drug to treat moderate to severe RA, followed by baricitinib [83, 84].

Glucocorticoids (GCs): Example: Methyl-prednisolone and Dexamethasone Glucocorticoids have been in use since70 years and treatment with glucocorticoids provides a variety of anti-inflammatory and immunosuppressive effects [85]. GCs act via different mechanisms. They reduce inflammation and symptoms of rheumatoid arthritis, improve physical function, and reduce disability. Glucocorticoids acts by inhibiting the migration of leukocytes at the site of inflammation, decrease the generation of IgG and cytokines from B cells and T cells and macrophages respectively, inhibit dendritic cell migration, differentiation, maturation, and antigen presentation, inhibit the activity of Th17 cells, enhances osteoclast maturation but inhibits osteoblast differentiation [86, 87]. Glucocorticoids are associated with several side effects when used in the long term. It can increase mortality and cause diabetes mellitus, osteoporosis, cardiovascular events, infections, myopathy, and weight gain. In this view of side effects, ACR recommended the short-term use of GCs in low doses and as a bridging therapy with csDMARDs. The use of GCs should be tapered as soon as csDMARDs reach their maximum effect, if clinically possible [88-91].

Non-Pharmacological Treatment for Rheumatoid Arthritis: Many drugs are available to manage RA, but their uses are associated with various adverse effects that lead to compromised quality of life (QOL) in RA patients. So, Non-pharmacological interventions play a vital role in improving the QOL of RA patients and help rehabilitate the patients [92].

Yoga: Yoga is a set of mind-body techniques that include breathing exercises, physical postures, and meditation that helps healthy people and patients suffering from autoimmune diseases like RA and osteoarthritis. Mind-body intervention has a significant impact on the Autonomic nervous system, shifting its balance to the parasympathetic system, which helps combat the negative effects of stress. Reduced stress in turn lowers the levels of inflammatory mediators. Yoga also influences the hypothalamic-pituitary-adrenal axis that, lowers cortisol levels, and improves the immune system functions [93]. Selvakumar Ganesan in his randomized clinical trial for 12 weeks, has proved that yoga helps in reducing disease activity, and level of IL-1α in serum and improves the sympathovagal balance in RA patients [94]. Previously Manoj Dash has proved in his research that yoga improves the hand's grip strength in RA patients [95]. Xiangling also documented in his systemic review and metaanalysis that yoga improves disease activity, physical functions, and hands grip strength in RA patients [96].

Surgery: It is the last option for the treatment of RA, which aims to restore the functions of joints, relieve pain, and correct and prevent future deformity. Surgery is recommended for patients with intractable joint pain due to joint destruction and cannot be managed by non-surgical treatments options [97]. Surgical procedures can be prophylactic or therapeutic. In prophylactic surgeries, inflamed synovial tissues are removed to improve joint functions and prevent tendon rupture. In therapeutic surgeries, joint fusions and joint replacements are used to relieve pain as joint destruction and tendon rupture already exist [98]. Toxicities and reappearance of symptoms after discontinuation of drugs are the major disadvantages of currently available synthetic medicines [99]. It has been proved that patients in pain who are suffering from RA are dissatisfied with the current available treatment and opt for complementary alternative medicines [100].

Herbal Treatment: Apart from synthetic drugs, non-pharmacological and surgical treatments, herbal therapies are also important for RA treatment. Owing to its cost effectiveness, better tolerability and various target of actions, phytotherapy proves to be beneficial for the treatment of RA. The presence of secondary metabolites in plants makes them useful for the treatment of various diseases, and thus, these herbal products are boon for RA patients. Herbal remedies used for RA treatment can act on multiple targets and relieve the patients. These herbal remedies can reduce the inflammatory responses by acting on multiple targets like, they suppresses TNFα level, Interleukins, cyclooxygenase, lipoxygenase, Nuclear factor-κβ and metalloproteinase [101].

TABLE 2: PHYTOCONSTITUENTS AND THEIR MECHANISM OF ACTION FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS

Component	Source	Family	Mechanism of action	Reference
Curcumin	*Curcuma longa*	Zingiberaceae	Curcumin induces apoptosis, Inhibits COX 2, prostaglandin E2, rapamycin pathway in mammals, RA induced infiltration of inflammatory cells in synovium and also reduces the levels of proinflammatory cytokines like IL-1β, TNF-α, NF-κβ, Activated protein-1, mitogen activated protein kinase,Matrix metalloproteinase (MMP)-1 and MMP-3	103 104
Gingerols, Zingerone, Cedrone	*Zingiber officinale*	Zingiberaceae	Inhibits osteoclast differentiation, decreases oxidative stress, NF-κβ, TGF-β, TNF-α, IL-6, IL-1β and Hs-CRP, increases IL-10 levels,inhibits COX-2, inhibits JAK3 Phosphorylation,	105 106 107 108
Berberine	*Berberis aristate*	Berberidaceae	Induces apoptosis in dendritic cells, inhibits IL-21/IL-21R mediated autophagy, IL-21/IL-21R mediated inflammatory proliferation	109 110
Calestrol Triptolide	*Tripterygium wilfordii*	Celastraceae	Calestrol inhibits activation of NF-κβ, endoplasmic reticulum calcium ATPase, TLR4 and modulates proinflammatory chemokines. Triptolide inhibits NF-κβ pathway, RANKL/ RANK/OPG signaling, COX-2, matrix metalloproteinase, cytokines and promotes VEGF driven angiogenesis.	111
Resveratrol	*Vitis vinifera*	Vitaceae	Inhibits TNF α induced IL-1β and MMP-3 production, MAPK signaling pathway, reduces ROS and suppresses angiogenesis.	112 113

IL: Interleukins, YGF-β: Transforming growth factor β, IL: Interleukins, COX: Cyclo-oxygenase, ATP: Adenosine triphosphate, TLR: Toll-like receptor, TNF: Tumor necrosis factor, NF-κβ: Nuclear factor, MMP:Matrix metalloproteinase, ROS: Reactive oxygen species, MAPK: Mitogen-activated protein kinase, Hs-CRP: high sensitive C-reactive protein, JAK: Janus kinase, RANKL/ RANK/OPG: Receptor activator of nuclear factor-κβ ligand- osteoprotegerin.

CONCLUSION: There are several Conventional approaches for the management of RA, but these approaches are very costly and cause an economic burden on the RA patients. Also, conventional approaches are associated with several side effects, low efficacy, and symptoms can also reappear after discontinuation of the medicines. Drugs Like NSAIDs can cause gastric disturbances, nephrotoxicity, and ulceration.

TNF α inhibitors can activate autoimmune reactions and hypersensitivity, and the use of biological agents could increase the chance of infections. Thus, in view of the shortcomings of synthetic medicines, herbal treatment, which is an alternative approach, can be used for the management of RA. Although extensive research is being carried out and proved that natural products are more promising for the treatment of RA, but there is still more scope for investigating various novel phytochemicals for their efficacy, mechanism of action, and safety for the treatment of RA. In a nutshell, early diagnosis, classification, and treatment of RA can prevent the patients from adverse disease outcomes. The herbal approach can be explored as an alternative treatment for the control of Rheumatoid arthritis.

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