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REVIEW

Natural Products and Traditional Herbal Medicines as Managerial Therapies to Combat Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a complex and challenging autoimmune disease characterized by chronic inflammation of the joints, discomfort, stiffness, functional impairment, and systemic complications that affect millions of people around the world. Despite advances in medication, controlling RA remains difficult due to its complicated pathophysiology and numerous clinical symptoms. Synthetic medications, while effective, frequently cause considerable adverse effects, necessitating the investigation of alternate therapeutic options. This study attempts to provide a complete overview of synthetic medications and natural items used to treat RA. It specifically investigates the pathophysiological mechanisms that underpin RA and the efficacy and safety profiles of synthetic pharmaceuticals. Synthetic medications, such as disease-modifying antirheumatic drugs (DMARDs), and biologics remain important treatments for RA, albeit with hazards. So to explore safer and more effective therapy for the treatment of RA, a need to exploit the possible therapeutic benefits of natural items such as antioxidants, plant secondary metabolites, and traditional herbal remedies arises. By encompassing a spectrum of insights, from the molecular level to holistic traditional practices, this review aims to provide a holistic understanding of the role of natural products and traditional herbal medicines in the managerial landscape of RA. Furthermore, it investigates the effect of nutrition in regulating inflammation and disease development in RA. Integrative techniques that use natural products present intriguing adjuvant therapy, delivering anti-inflammatory, analgesic, and immunomodulatory effects with potentially fewer side effects. Understanding the interaction of synthetic medications and natural products, as well as the role of nutrition, can help enhance RA treatment regimens, improve patient outcomes, and reduce treatment-related problems. This study is a valuable resource for doctors, researchers, and patients looking for evidence-based methods for RA care. The synthesis of this knowledge contributes to the ongoing pursuit of enhanced therapeutic strategies, fostering improved outcomes and quality of life for individuals grappling with rheumatoid arthritis.

Keywords Rheumatoid treatment · Diet · Antioxidants

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that develops in humans when the immune system works against the body. It mainly develops in the synovium lining of the bone joints, which can result in swelling and inflammation of the synovium. Inflammation of synovial joints can cause permanent damage to cartilage and bone. Furthermore, due to inflammation, the joint gradually loses its normal shape and reduces bone strength and the ability to function properly [1]. In addition, the tendons and ligaments responsible for joint stability can weaken over time. Typically, RA affects the smaller joints of the fingers, wrists, and ankles, but it can also affect various other parts of the body, including the eyes, lungs, blood vessels, heart, and

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skin. According to the World Health Organisation (WHO), 18 million people suffered from RA in 2019. RA is more prevalent among adults over the age of 50, with the majority among female populations. According to studies, people suffering from RA are around 0.1% of the world's population. RA affects more than 70% of women and 55% of people over the age of 55 years. Additionally, 13 million people suffer from RA at severity levels (moderate or severe). In India, approximately 0.92% of the adult population have RA [2, 3].

The precise cause of RA remains unclear, but several factors contribute to its development. Previous research revealed that the cause and progression of RA depend on environmental, genetic, and infections. The other minor factors that stimulate the progression of RA include synovial damage, hyperplasia, and autoantigen modification. Environmental factors such as obesity, smoking, and specific pathogens such as *Porphyromonas gingivalis* can trigger RA factors. Genetic factors such as anomalies in cytokine synthesis, signal transduction, and T- and B-cell activity led to immune cell activation. Epigenetic modifications and genetic variations that affect the antigen response also play an essential role in the development of RA [4, 5]. The synovial damage and hyperplasia processes result in inflammatory conditions that aid in damaging synovial fibroblasts and causing them to grow abnormally. At the same time, autoantigen modification is a process known as citrullination, which eventually alters autoantigens. This alteration leads to neoepitopes because of the modified surface charge and the higher susceptibility to proteolytic degradation. This process leads to the development of RA [6]. A schematic representation of the potential cause of RA is given in Fig. 1. These factors stimulate and result in inflammation of the joints. At the same time, the body begins to oppose an invader that is not there.

Unlike RA, osteoarthritis is a common condition typically associated with joint wear and tear that occurs as people age. Unlike osteoarthritis, RA is an autoimmune disorder that can lead to disability if not adequately treated [7].

The scrutiny of RA causation and the underlying mechanisms, coupled with an in-depth analysis of synthetic drugs, biologics, and compounds that undergo clinical evaluation, underscores the need for a diversified therapeutic approach. The pivotal focus on natural products unveils a promising avenue to elucidate the molecular intricacies by which antioxidants and plant secondary metabolites contribute to RA mitigation. Traditional herbal medicine and extracts, subjected to rigorous examination, offer valuable insight into their pharmacological efficacy and established roles in the management of RA. Furthermore, giving recommended diets offers a pragmatic avenue for individuals to actively participate in their well-being. The review will improve knowledge, well-being, and outcomes for individuals living with RA.

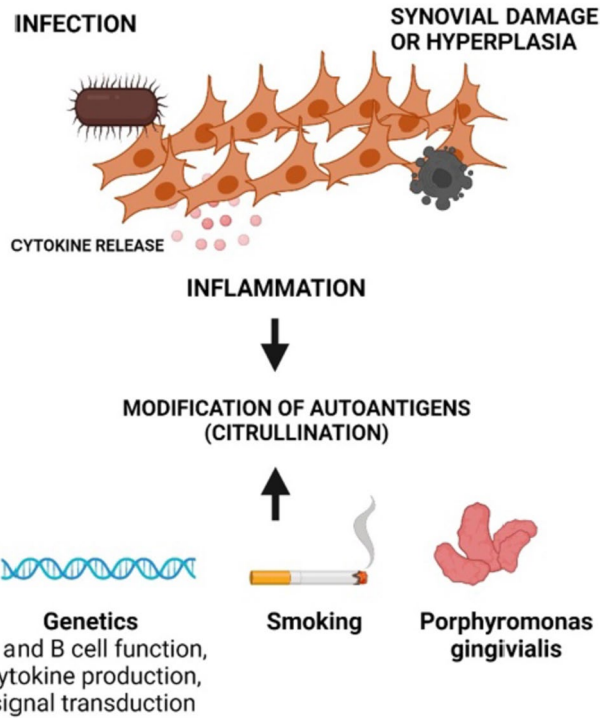


Fig. 1 Potential causes of RA

Pathophysiology of RA

Immune dysregulation leads to autoimmunity in RA, which is thought to develop when genetically susceptible individuals are exposed to environmental triggers. RA can affect several organ systems, including blood vessels. The primary target site of autoimmunity is the cellular lining of the joints, known as the synovium. Both adaptive and innate immune responses contribute to the development of RA, with T-cell lymphocytes, particularly Th1 and Th17 cells, prevalent in the synovium. The stimulated antigen-presenting in the lymph node interacts with T and Bursa-derived cells (B cells), which increases the production of chemokines and cytokines, lymphocyte differentiation, and the formation of autoantibodies. T and B cells then migrate to the joint and interact with synoviocytes, macrophages, dendritic cells, and osteoclasts. As a result, more inflammatory cells enter the joint space, as well as the production of degradative enzymes, inflammatory cytokines (like TNF-alpha, IL-1, and IL-6), synoviocyte hyperplasia, and neoangiogenesis. To combat this perceived invader, Janus kinases and cytokines communicate during the inflammatory cycle, often causing further inflammation [8, 9]. Within the inflamed joint, specific cells such as macrophages, fibroblasts, and osteoclasts begin to damage cartilage and bone, contributing to the progression of the disease [10]. Synovitis is the result of these interactions

and presents clinically as swollen, inflamed, and painful joints. Inflammatory destructive pannus is the result of untreated synovitis; damages bone, cartilage, and other articular tissues; and results in chronic pain and bone and joint deformities [8, 9]. A pictorial representation illustrating the pathophysiology of RA is given in Fig. 2.

Specific blood tests, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibodies, are used in the diagnosis of RA [11]. Laboratory markers are essential, including elevated levels of CRP and ESR in blood serum, as well as detection of specific autoantibodies for RA, all of which are carefully examined by a medical professional as part of the diagnostic process. Furthermore, to diagnose and monitor the progression of RA in patients, medical professionals often recommend performing ultrasound and magnetic resonance imaging. In addition, the diagnosis of RA includes a complete assessment of the patient's condition. This assessment considers various factors, including the patient's symptoms, such as recent joint pain and swelling, morning stiffness, family history, and joint ultrasound sonography [12, 13].

Treatment for RA

The exact reason for RA is not known, but once damage to bone joints occurs, it cannot be reversed by anti-RA therapy. However, there are various drugs, supplements, and therapies available to minimize the effects of RA symptoms. The primary objective of RA treatment is to stop this inflammatory process and prevent further joint damage [2, 3]. Fortunately, there are several classes of drugs available that can reduce RA symptoms. Possible forms of treatment include disease-modifying antirheumatic drugs (DMARDs), methotrexate being a standard first-line therapy for RA. Furthermore, targeted synthetic DMARDs inhibit various kinases, including JAK or MAPK. Other treatment approaches include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, joint stress reduction, physical and occupational therapy, and, when necessary, surgical

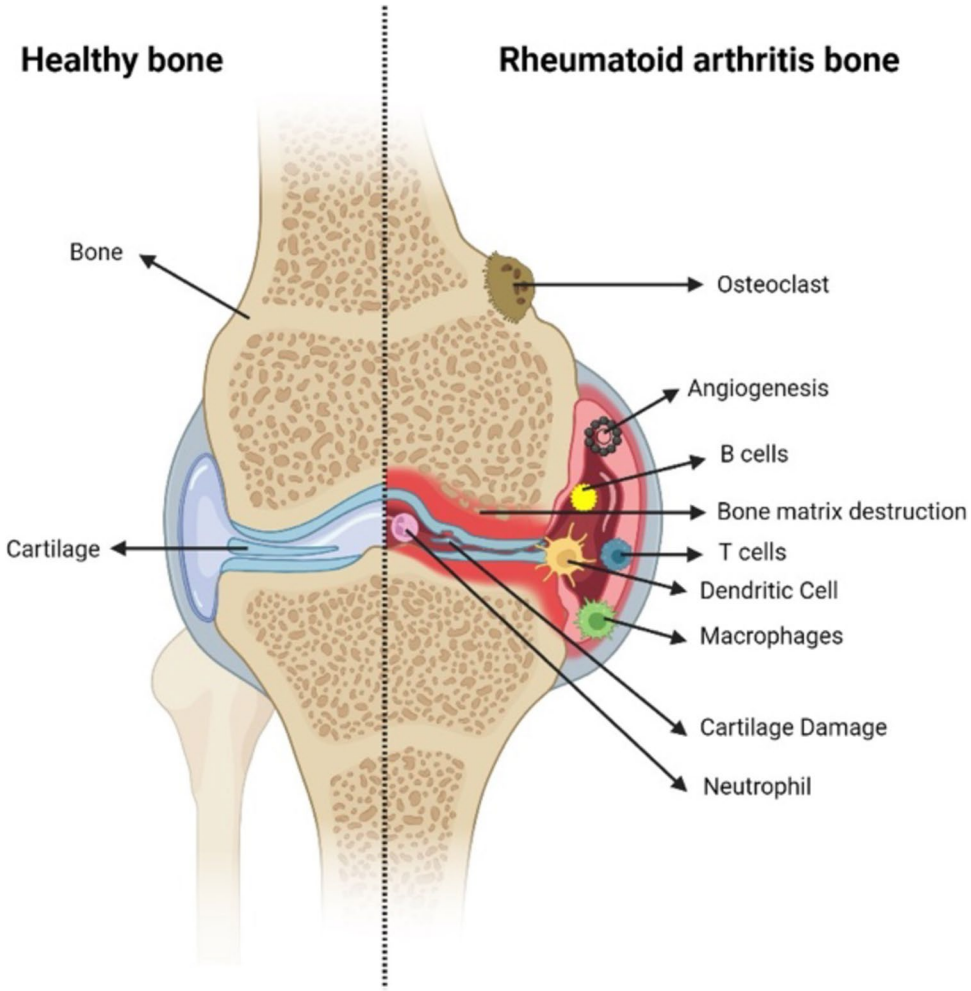


Fig. 2 A visual representation illustrating the pathophysiology of RA. A healthy synovial joint is depicted on the left side of the diagram. On the right side, it highlights the critical pathophysiological mechanisms that lead to the development of the RA condition

intervention. These conventional medications are effective against RA symptoms and suppress inflammatory factors in vivo but show minimal effects on the improvement of the disease [14]. These drugs show some adverse side effects, such as substantial hepatotoxicity, cardiovascular disease, and others, which limit their therapeutic and clinical use [15]. Although these treatments can initially alleviate symptoms, people can eventually lose their ability to them; in that case, biologics are prescribed. Biologics are a class of medications that target specific parts of the immune system involved in inflammation and joint damage in RA. Biologics can significantly improve symptoms and slow disease progression. However, these biologics are associated with increased risks of severe infections such as tuberculosis and reactivation of hepatitis B and some of the rare side effects such as drug-induced lupus, demyelinating diseases, and lymphoma. Compared to DMARDs, biologics substantially increase treatment costs [16]. In severe cases, anti-TNF/Il6 biologics are prescribed, but their enhanced therapeutic potential is offset by reduced patient compliance due to invasive administration and a variety of adverse effects. These adverse effects include the gradual onset of immune deficiencies or autoimmune flares and the development of antidrug antibodies, resulting in decreased treatment effectiveness [17]. Treatment for RA, including synthetic drugs and biologics, is given in Table 1, and a list of compounds under clinical evaluation for the treatment of RA is shown in Table 2.

Treating RA is associated with challenges, such as a complex autoimmune nature, variability in the disease course, difficulty in early diagnosis, complex medication regimens, side effects of medications, cost of biologics, patient compliance, joint damage prevention, management of comorbidities, impact on mental health, and access to specialized care. RA management is a complex and personalized process that requires careful monitoring and coordination among healthcare providers. Given all the limitations, there is a pressing need for safer, more effective, and more affordable therapy options to alleviate and cure RA. A promising approach can be natural products such as traditional herbal products; it has been the result of a thoughtful and meticulous investigation of medications that have been used for many years and are known to be safer, with easy access to the general public [15].

Natural Products as a Promising Therapy to Tackle RA

Natural products, such as traditional herbal drugs, have potential benefits for the treatment of RA. They have fewer side effects than synthetic drugs and biologics and offer anti-inflammatory properties and pain relief. Herbal products are often used alongside conventional drugs as complementary therapies. Numerous extracts, active components, and isolated compounds from traditional herbal medicines (THMs), including alkaloids, flavonoids, triterpenes, and phenolic acids, have shown potential anti-RA properties based on emerging data and research. These bioactive substances alleviate RA symptoms by interacting with various targets involved in immune regulation, oxidative stress, miRNA, angiogenesis, and inflammatory responses [38].

Managing RA with Antioxidants

Several studies suggested the substantial involvement of oxidative stress involved in the development of RA. Oxidative stress, defined as an imbalance between the creation of harmful reactive oxygen species (ROS) and the body's ability to mitigate their impact, has been linked to inflammation in tissue and is responsible for the harm in RA. In addition to inflammatory cytokines and matrix metalloproteinases, RA causes an excess release of free radicals. This excessive release contributes to inflammation and facilitates interactions among host cells, including chondrocytes, fibroblasts, and osteoclasts [39, 40]. Due to inflammatory responses, inflammatory cells (neutrophils) produce oxidant substances. In the plasma membrane, neutrophils have NADPH oxidase enzyme. Superoxide radicals of O_2 are a form of ROS produced when bacteria and immunological complexes stimulate cells. Other ROS are produced as a result of radical reactions [41]. Monocytes, macrophages, and granulocytes produce free radicals. Monocytes, for example, generate 2.7 times more oxygen radicals in individuals with RA than in healthy individuals. During the electron transport process, oxidative phosphorylation is a source of mitochondrial reactive oxygen species (mtROS) within mitochondria. In addition to ROS, including peroxide, superoxide, and hydroxyl, free radicals also encompass RNS. The production of reactive nitrogen and oxygen species is a defense mechanism of the body against various bacterial infections, but their continuous excess results in the degeneration of cartilage and bone. Free radicals can damage biological molecules such as proteins, low-density lipoprotein (LDL), lipids, and DNA; they can also damage unsaturated fatty acids in cell membranes, leading to loss of cellular integrity and functional changes in cells' receptors and enzymes [42, 43]. Through the MAPK pathway, mtROS promotes inflammatory cytokines (IL-6 s and TNF-α). To some extent, increased ROS production and loss in the body's capacity to remove them are responsible for the progression of RA. The claim mentioned above is supported by the metabolites induced by free radicals observed in synovial fluid [44].

The measurement of total antioxidant capacity (TAC) can be used to assess serum antioxidant status. A lower TAC indicates an increased free radical activity. In patients with RA, the antioxidant defense system experiences decreased

Table 1 Synthetic drugs and biologics as a treatment for RA

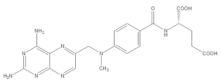
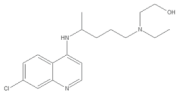
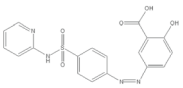
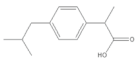
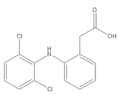
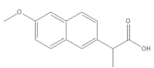
Category	Compounds/biologics	Mode of actions	Side effects	Ref
1. Disease-modifying antirheumatic drugs (DMARDs	 Methotrexate	It inhibits adenosine release, reduces neutrophil adhesion, and suppresses cell-mediated immunity. It also inhibits dihydrofolate reductase, an enzyme involved in folate metabolism	Nausea, vomiting, abnormal liver function, suppression of bone marrow	[18]
	 Azathioprine	It exhibits immunosuppressive effects by inhibiting lymphocyte proliferation	Nausea, vomiting, suppression of the bone marrow, increased risk of infection	[18]
	 Hydroxychloroquine	Immunomodulatory effects by inhibiting TLR signaling and antigen presentation	Nausea, vision changes, skin rashes	[18]
	 Sulfasalazine	It combines sulfa antibiotic with 5-aminosalicylic acid and is responsible for the anti-inflammatory effect. It also provides immunomodulatory effects by preventing oxidative damage and inhibiting the activation of the nuclear factor kappa B (NF- κB) activation	Nausea, gastrointestinal disturbances, headache, rash	[19]
2. NSAIDS	 Aspirin	NSAIDs work by inhibiting enzymes called cyclooxygenases (COXs). These enzymes are involved in the production of prostaglandins, which are inflammatory molecules. By blocking COX, NSAIDs reduce prostaglandin production, leading to decreased inflammation, pain, and fever	GI problems such as stomach irritation, ulcers, GI bleeding, cardiovascular events, renal dysfunction, and some patients may experience allergic reactions	[20]
	 Ibuprofen			
	 Diclofenac			
	 Naproxen			
3. Biologics TNF-α antagonist	Etanercept Infliximab Adalimumab Golimumab Certolizumab Etanercept	These biologics target tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine. By inhibiting TNF-α, they reduce inflammation and slow the progression of RA	Injection site reactions, increased risk of infections, and, in some cases, development of antibodies against the drug	[18]
IL-1 antagonist	Anakinra	Inhibits the binding of IL-1 to the receptor, leading to reduced production of pro-inflammatory molecules	Injection site reactions, upper respiratory tract infections, headache, gastrointestinal symptoms, elevated liver enzymes	[21]
IL-6 inhibitors	Tocilizumab Sarilumab	It inhibits the action of IL-6, another pro-inflammatory cytokine, reducing inflammation and joint damage	Increased risk of infections, elevated liver enzymes, and abnormal lipid levels	[18]
T-cell modulating agent	Abatacept	Binds CD80/CD86 to antigen-presenting cells, blocking interaction with CD28 on T cells, and reducing inflammation	Upper respiratory tract infections, headache, and hypersensitivity reactions	[18]
B-lymphocyte depletor	Rituximab	Binds CD20 to B cells, which affects the immune response and inflammation. By causing B-cell depletion, it reduces inflammation	Infusion reactions, increased risk of infections, and potential long-term effects on the immune system	[18]

Table 2 A list of compounds under clinical evaluations to treat RA

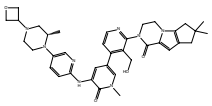
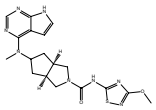
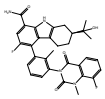
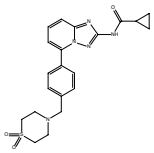
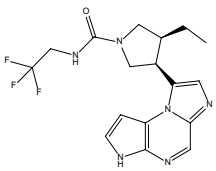
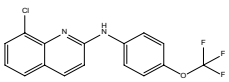
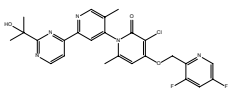
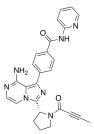
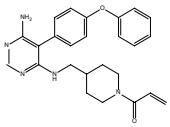
S. no	Drugs	Mode of actions	Current status	Ref
1.	 Fenebrutinib	Fenebrutinib is a Bruton tyrosine kinase (BTK) inhibitor. It inhibits FcγR signaling in B cells and myeloid cells, respectively	Phase 2	[22]
2.	 SHR0302 (Ivarmacitinib)	Ivarmacitinib is a Janus kinase-1 inhibitor. It inhibits the proliferation of T and B cells and FLS, down-regulated cytokines TNF-α, IL-1β, IL-17, and antibodies such as IgG1 and IgG2a levels. Furthermore, it suppressed the proportion of Th17 and total B and inhibited the phosphorylation of JAK1-STAT3	Phase 2	[23]
3.	 BMS-986142	A reversible, non-covalent Bruton's tyrosine kinase inhibitor. Inhibit antigen-dependent B-cell signaling without depleting B cells	Phase 2	[24]
4.	 Filgotinib	Filgotinib is a Janus kinase inhibitor. Selectively inhibits JAK1 phosphorylation and prevents STAT activation, reducing pro-inflammatory cytokine signaling	Phase 2b/3	[25]
5.	 Upadacitinib	Upadacitinib is a Janus kinase (JAK) 1 inhibitor. Inhibition of JAKs further hinders the transduction of growth factor- and cytokine-mediated signals intracellularly by the JAK-STAT pathway	Phase 3	[26]
6.	 ABX464 (obefazimod)	Obefazimod is a TNF-α inhibitor. It upregulates the biogenesis of the microRNA-124 mRNA inhibitor and can act as a natural break in the production of various inflammatory mediators involved in inflammatory diseases	Phase 2a	[27]
7.	KIC-0101	KIC-0101 suppresses the NF-κB pathway and induction of pro-inflammatory cytokines		[28]
8.	SM03	SM03 decreased the TLR4-induced NF-κB response by decreasing the promotion of autoimmunity and inflammation	Phase 2	[29]
9.	 ATI-450 (Zunsemetinib)	Zunsemetinib causes a reduction in TNF-α, macrophage inflammatory protein 1β, IL-6, and IL-8 through the signaling pathway of p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway	Phase 2a	[30]
10.	 Acalabrutinib	Acalabrutinib is an irreversible Bruton tyrosine kinase inhibitor. It covalently binds to Cys481 in the ATP-binding pocket of BTK, leading to inhibition of BTK enzyme activity	Phase 2	[31]
11.	 Evobrutinib	Evobrutinib is a Bruton's tyrosine kinase inhibitor	Phase 2	[32]
12.	Olokizumab	Olokizumab is a Janus kinase inhibitor. It is an IL-6 inhibitor and blocks the formation of the extracellular signaling complex, consequently inhibiting transmembrane signaling	Phase 3	[33]
13.	Ozoralizumab	Ozoralizumab is a tumor necrosis factor-alpha (TNF-α) inhibitor	Phase 3	[34]
14.	Otilimab	It is an anti-granulocyte–macrophage colony-stimulating factor antibody (GM-CSF)	Phase 3	[35]
15.	KPL-404	KPL-404 acts as a CD40 antagonist	Phase 2	[36]

Table 2 (continued)

S. no	Drugs	Mode of actions	Current status	Ref
16.	ABBV-3373 (adalimumab)	Adalimumab is an antagonism of TNF	Phase 2a	[37]
17.	TAS5315	TAS5315 is an irreversible Bruton tyrosine kinase inhibitor	Phase 2	[31]

levels of TAC, antioxidant enzymes (superoxide dismutase, glutathione peroxidase, and catalase), and high malondialdehyde secretion [45]. Epidemiologic studies have also shown an unfavorable correlation between dietary antioxidant intake and the appearance of RA. Dietary intake of antioxidants is lower in RA patients, and their blood levels showed decreased antioxidant concentrations. Compared to a healthy person, in RA patients, synovial fluid and serum contain lower antioxidant levels. Yet the ongoing generation of free radicals in inflamed joints results in the downside of the antioxidant system (both enzymatic and non-enzymatic), leading to tissue destruction [46]. A possible explanation for this condition could be the inadequate intake of natural antioxidants from food, as we discovered from the literature that the dietary intake of micronutrients with vitamin E (alpha-tocopherol), vitamin C, provitamin A, selenium, zinc, and beta-carotene was less than the recommended amounts in RA patients. The patient's food intake is affected by loss of appetite and impaired absorption and metabolism of dietary micronutrients. Other causes may include the inability to prepare food and the avoidance of certain foods due to fictitious diets [47]. These are some of the antioxidant supplements that have been researched concerning RA.

Vitamins as Antioxidants and Their Managerial Role in RA Therapy

Vitamin C is a potent antioxidant. It is present in oranges, grapefruits, lemons, strawberries, kiwis, bell peppers, and broccoli. Some studies have suggested that it might help reduce inflammation and oxidative stress in patients with RA. Vitamin C is capable of neutralizing harmful free radicals. Additionally, vitamin C is vital for collagen production, a structural protein in cartilage, connective tissues, and bones. Furthermore, adequate vitamin C intake can support tissue repair and potentially decelerate the progression of joint deterioration [48]. Vitamin C has the potential to improve iron absorption without heme and may also impact the absorption of other minerals and medications, including NSAIDs and DMARDs, frequently used in the treatment of RA [49].

Vitamin E is a fat-soluble protein that has been investigated for its potential anti-inflammatory properties and protects cells and tissues from oxidative damage. It is commonly found in nuts, including almonds and hazelnuts, seeds such as sunflower seeds and pumpkin seeds, spinach, avocados, and vegetable oils [50]. Vitamin E, particularly alpha-tocopherol, is a powerful antioxidant that can be beneficial in neutralizing free radicals. The antioxidant properties of vitamin E can help decrease oxidative stress and protect joint tissues. Vitamin E may have a mild analgesic (pain reliever) effect. Although it is not a substitute for RA medications, it can contribute to overall pain management when used as part of a comprehensive treatment plan [51].

Beta-carotene is an antioxidant and belongs to a class of carotenoids. Foods rich in beta-carotene, a precursor to vitamin A, include carrots, sweet potatoes, butternut squash, and dark leafy greens such as spinach and kale. Beta-carotene acts as a potential antioxidant, countering free radicals, and highly reactive molecules that can foster oxidative stress and tissue harm. In RA, where oxidative stress can induce joint damage and inflammation, reducing it could prove advantageous for those affected. Moreover, beta-carotene is essential for a healthy immune system. Some research suggests that a diet rich in carotenoids, including beta-carotene, may have mild anti-inflammatory effects [52].

Elements as Antioxidants and Their Managerial Role in RA Therapy

Selenium is a trace mineral that acts as an antioxidant. Some studies have explored its potential benefits in people with RA conditions. Selenium is found in foods such as nuts, fish, and whole grains [53]. Selenium is a component of selenoproteins, including glutathione peroxidases (GPx), which function as antioxidants in the body. These selenoproteins aid in counteracting detrimental free radicals and diminishing oxidative stress. In RA, oxidative stress can contribute to joint inflammation and damage, and selenium's antioxidant properties can help mitigate these effects. Selenium is crucial for supporting joint health by diminishing inflammation and curbing oxidative damage within the joints. It has the potential to decelerate the progression of joint damage in RA [54].

Zinc is a mineral found in lean meats, nuts, and legumes. It supports the immune system and helps to repair tissues. It is a cofactor for multiple antioxidant enzymes, including superoxide dismutase (SOD), which helps neutralize harmful superoxide radicals in the body. These enzymes work to counteract oxidative stress and reduce the detrimental impacts of free radicals, which are implicated in RA inflammation and joint damage [55]. Moreover, zinc is essential to maintain a healthy immune system. In RA, the immune system becomes disrupted, leading to chronic inflammation and joint tissue attacks. Adequate

Table 3 Secondary plant metabolites with a managerial role in RA therapy and their mechanism of action

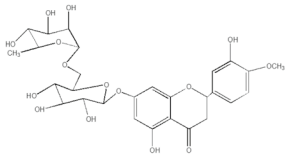
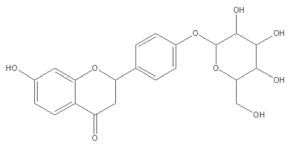
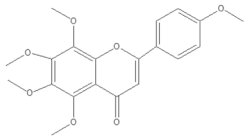
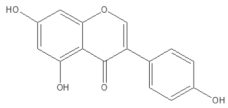
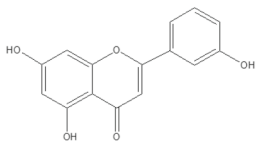
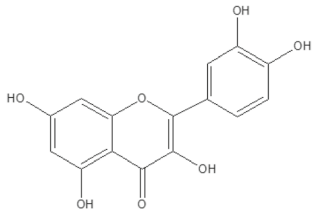
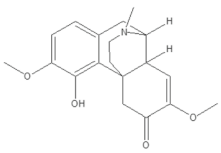
S. No	Chemical class	Compound	Mechanism of action	Ref
1.	Flavonoid	 Hesperidin *Citrus aurantium* L	It reduces oxidative stress. In addition, it inhibits inflammation in synovial cells and alters macrophage polarization by downregulating the PI3K/AKT pathway	[59]
2.		 Liquiritin *Glycyrrhiza uralensis* Fisch	It suppresses angiogenesis, reduces inflammation, and blocks the MAPK signaling pathway	1. [60]
3.		 Tangeretin *Citrus reticulata* Blanco	Promoting the nuclear erythroid 2-related factor 2 (Nrf-2) signaling pathway effectively mitigates oxidative stress and reduces inflammation	2. [61]
4.		 Genistein Leguminous plants	It partially inhibits the production of vascular endothelial growth factor (VEGF) and IL-6-induced angiogenesis, achieved by modulating the Janus kinase 2 (JAK2)/ STAT3 pathway	[62]
5.		 Apigenin *Apium graveolens* L	Limits the migration of dendritic cells (DCs) maturation, preventing inflammation, and inducing apoptosis. In addition, it limits synovial hyperplasia, osteoclastogenesis, and angiogenesis	[63]
6.		 Quercetin *Tussilago farfara* L./*Taxillus sutchuensis* (Lecomte) Danser	Prevent neutrophil infiltration and decrease inflammatory cytokine levels in the blood	[64]
7.	Alkaloid	 Sinomenine *Sinomenium acutum* (Thunb.) Rehd. Et Wils	It hinders the process of angiogenesis	[65]

Table 3 (continued)

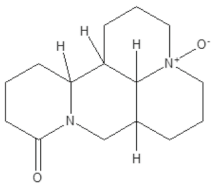
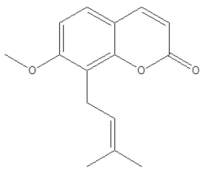
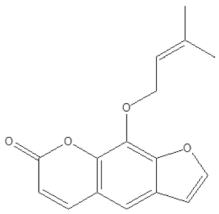
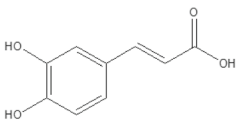
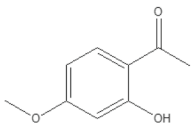
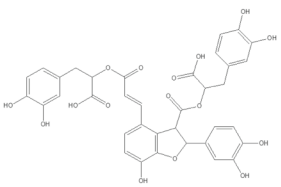
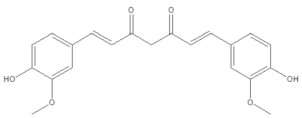
S. No	Chemical class	Compound	Mechanism of action	Ref
8.		 Oxymatrine *Sophora flavescens* Ait	Blocks the activation of NF-κB	[66]
9.	Coumarin	 Osthole *Cnidium monnieri* (L.) Cusson	It inhibits cell stress and inflammation	[67]
10.		 Imperatorin *Angelica dahurica*	Blocks NF-κB and MAPK pathways to inhibit proliferation, migration, and inflammation	3. [68]
11.	Phenolic compound	 Caffeic acid *Solidago decurrens* Lour	It inhibits the phosphorylation of NF-κB inhibitor kinase (IκB kinase/IKK) α/β and IκBα. Additionally, it targets the chitinase-3-like protein-1, angiogenesis, and inflammatory signals	[69, 70]
12.		 Paeonol *Paeonia lactiflora* Pal	It inhibits miR-155 and enhances its target FOXO3	4. [71]
13.		 Salvianolic acid B *Salvia miltiorrhiza* Bunge	Enhances miR-142-3p and alters the NF-κB and JNK pathways	5. [72]
14.		 Curcumin *Curcuma longa* L	It prevents the expression or activity of pro-inflammatory mediators like NF-κB, AP-1 (activated protein), and MAPKs	[73]

Table 3 (continued)

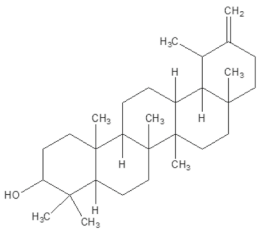
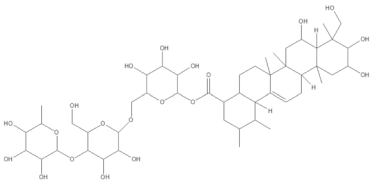
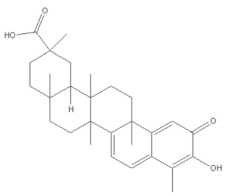
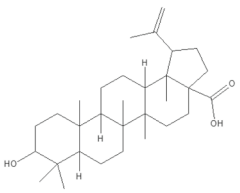
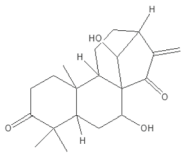
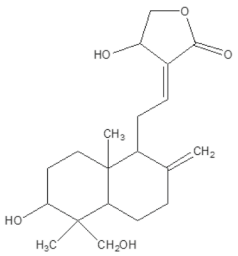
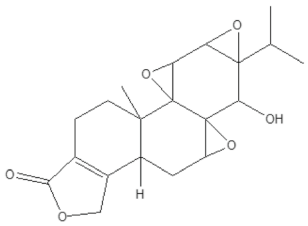
S. No	Chemical class	Compound	Mechanism of action	Ref
15.	Triterpenoid	 Taraxasterol *Taraxacum mongolicum*	NF-κB activation of NF-κB was hindered by altering IκB, IκB kinase, and TAK1. It suppresses NLRP3 (NOD-like receptor protein 3) inflammasomes by inhibiting NLRP3, an apoptosis-associated speck-like protein that contains a C-terminal caspase recruitment domain, and caspase-1	[74]
16.		 Madecassoside *Centella asiatica* (L.) Urb	It prevents the NF-κB-mediated matrix from being activated	[75]
17.		 Celastrol *Tripterygium wilfordii* Hook F	It decreases oxidative stress	[76]
18.		 Betulinic acid *E. ulmoides*	It prevents NF-κB	[77]
19.	Diterpenoids	 Glaucocalyxin *Rabdosia japonica* var. Glaucocalyx	It deactivates the STAT3 pathway	[78]
20.		 Andrographolide *Andrographis paniculata* (Burm. f.) Nees	In the presence of LPS, neutrophil apoptosis accelerates. PMA (phorbol myristate acetate)—induced NETosis (it is the formation of neutrophil extracellular traps). In addition, it suppresses inflammation and oxidation	[79]

Table 3 (continued)

S. No	Chemical class	Compound	Mechanism of action	Ref
21.		 Triptolide *Tripterygium wilfordii* Hook F	Through suppression of osteoclast activity and increased apoptosis of OCP	[80]

zinc levels may support immune function and help modulate the autoimmune response observed in RA. Zinc synthesizes collagen. Furthermore, sufficient zinc levels in the blood can support tissue repair and potentially slow the progression of joint damage [56].

Fatty Acids as Antioxidants and Their Managerial Role in RA Therapy

Omega-3 fatty acids are found in fatty fish such as salmon, mackerel, sardines, flaxseeds, and walnuts and have anti-inflammatory properties. Some research suggests that omega-3 fatty acids may help reduce inflammation and joint pain in RA. Omega-3 fatty acids (specifically EPA and DHA) have been shown to reduce inflammation in the body. It can regulate the immune response and reduce the generation of pro-inflammatory substances, which can alleviate RA symptoms [57]. Additionally, omega-3 fatty acids have well-documented cardiovascular benefits, such as reducing triglycerides, improving blood vessel function, and potentially lowering the risk of heart disease, which can be particularly relevant for individuals with RA [58].

Plant Secondary Metabolites as a Managerial Role in RA Therapy

Certain secondary plant metabolites with managerial roles in RA therapy are given in Table 3, and peptides as potential RA therapy are shown in Table 4.

The plausible mechanism of action of secondary metabolites as anti-RA is depicted in Fig. 3.

Traditional Herbal Medicines and Herbal Extracts as a Managerial Therapy of RA

Green Tea

Green tea extract comprises antioxidants called catechins, with the most abundant and well-studied catechin being epigallocatechin gallate (EGCG). Green tea extract has gained attention for its possible health benefits, including its antioxidant and anti-inflammatory properties. The anti-inflammatory properties of green tea extract could potentially reduce inflammation and relieve RA symptoms [91]. Green tea extract may also support the immune system by modulating immune cell activity. Polyphenols from green tea, including EGCG, can inhibit enzyme activity involved in oxidative stress, such as xanthine oxidase and myeloperoxidase. By inhibiting these enzymes, green tea extract may help reduce oxidative damage [92].

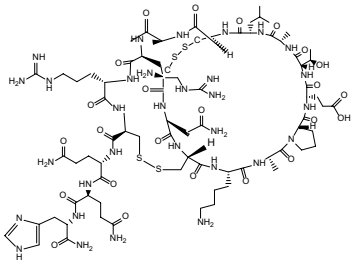
Willow Bark

Willow bark, which has been used for generations to reduce pain and inflammation, is likely to be used as a complementary therapy for the treatment of RA. Bark extracts have been used in areas including South America, Egypt, Classical Greece, and China, according to historical documents [93]. Willow bark contains salicin, a precursor to salicylic acid, which is also found as an active component in aspirin. This substance inhibits the enzymes involved in prostaglandin formation, which reduces inflammation and pain. Salicylic acid and other components of willow bark contribute to its anti-inflammatory actions, which may help patients with RA with joint swelling, stiffness, and discomfort. Like aspirin, willow bark also helps to lower body temperature, offering relief from RA-related fever [94].

Stinging Nettle

Stinging nettle (*Urtica dioica*) belongs to a rare herbaceous perennial flower plant with stinging hairs native to Asia, Africa, and Europe. The nettle leaf extract complimented each other in the experimental, clinical, and trial phases. It is a well-known plant with a long history of using stems, leaves, and roots. It is used as a source of energy, such as soup or curry, as well as fiber, and as a medicinal herb. Nettle leaf extracts are used as anti-inflammatory treatments for RA [95]. Nettle includes several anti-inflammatory substances, including histamine, serotonin, and chlorogenic acid. These can help

Table 4 Peptides that act against RA and their mechanism of action and their role

S. no	Peptide	Structure/sequence	Mechanism of action	Ref
1.	Apitoxin Source: *Apis mellifera*		Apitoxin causes downregulation of IL-6 and induces NF-κB activation. In addition, it leads to the suppression of antiapoptotic genes and a concomitant increase in the expression levels of pro-apoptotic factors and caspase activity	[81]
2.	Agkistrodon Source: *Agkistrodon acutus*	NSLVLRGRMRDVKVRDDGRKSP-SHHSKFSGGTRNWQKLVKL	Agkistrodon suppresses the expression of TNF-α, IL-1β, and IL-6 inflammatory cytokines It also attenuates inflammation and inhibits cartilage destruction and bone erosion	[82]
3.	GLPP Source: *Ganoderma lucidum*	DRVSIYGWG and ALLSISSF	GLPP inhibits the NF-κB and MAPK pathways. It decreased the protein expression of TNF-α, IL-1β, IL-6, matrix metalloproteinase (MMP)2, MMP9, MMP13, BCL-2, OPN, β-catenin, and hypoxia-inducible factor (HIF)-1α	[83]
4.	Psalmotoxin 1 Source: Venom of the southern spider tarantula *Psalmopoeus cambridgei*	EDCIPKWKGCVNRHGDCCE-GLECWKRRRSFEVCVPKTPKT	Psalmotoxin 1 reversed the effects of extracellular acidosis in articular chondrocytes It also reduces the expression levels of ASC and caspase-1 in articular chondrocytes. Furthermore, it attenuates extracellular acidosis-induced cellular pyroptosis in articular chondrocytes by regulating NLRP3	[84]
5.	Scolopendrasin IX Source: *Scolopendra subspinipes mutilans*	MCKYFIKIVSKSAKK-CONH2	Scolopendrasin IX strongly inhibits the recruitment of inflammatory cells into the synovium. Blocks joint destruction and restores articular cartilage	[85]
6.	SJMHE1 Source: *Schistosoma japonicum*	VPGGGTALLRCIPVLDTLSTKNED	SJMHE1 down-regulates critical cytokines such as interferon-γ (IFN-γ), TNF-α, IL-6, IL-17, and IL-22, and at the same time, it upregulates the inhibitory cytokine IL-10, Tgf-b1 mRNA, and CD4 +, CD25 +, Foxp3 +, Tregs. Block the progression of joint erosion	[86]
7.	Paramyosin Source: *Trichinella spiralis*	VSMGKSLSSKVYVM	It binds to C9 and inhibits MAC assembly (membrane attack complex) assembly	[87]
8.	APHC3 Source: *Heteractis crispa*	GSICLEPKVVGPCTAYFPRFYFN-SETGKCTPFIYGGCEGNGNNFETL-RACGICRA	It decreased IL-1b concentration in synovial fluid, reduced inflammatory changes in joints, and prevented the progression of cartilage degradation	[88]
9.	Wasp venom Source: *Vespa magnifica*		Modulates the JAK-STAT signaling pathways	[89]
10.	Enzymatic hydrolysate of tuna elastin Source: *Tuna bulbus cordis*	Leu-Asp-Leu-Asp-Asp-Phe (LDLDDF) Phe-Ser-Phe-Leu (FSFL)	It reduced inflammatory markers such as IL-1β, IL-6, TNF-α and IL-17. In addition, it protects bone from inflammatory damage	[90]

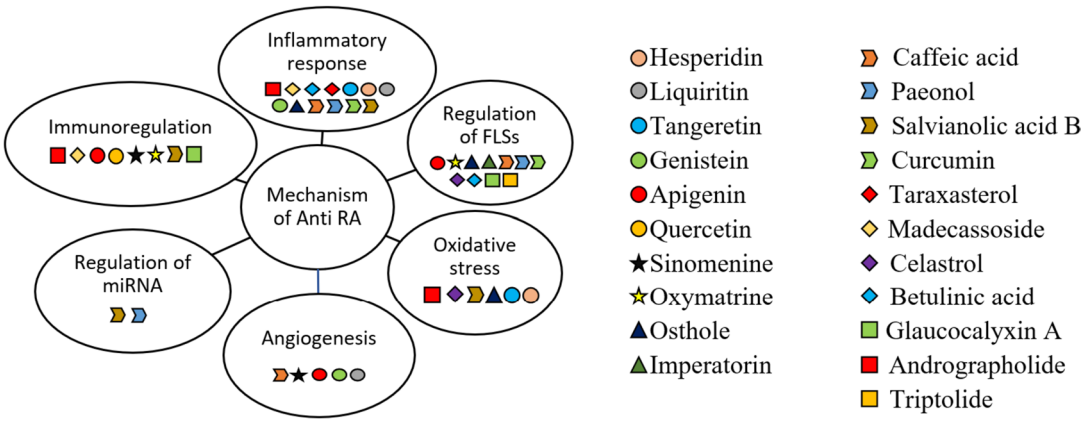


Fig. 3 Plausible mechanism of action of plant secondary metabolites as anti-RA

RA sufferers minimize joint swelling, pain, and stiffness. The stinging sensation caused by the hairs of the nettles functions as a counterirritant, diverting the brain's attention away from the discomfort caused by inflamed joints. Nettle may also have an indirect effect on pain pathways. Nettle acts as a diuretic, encouraging the elimination of excess fluids and toxins that could contribute to inflammation in patients with RA [96].

Thunder God Vine

Thunder god vine (*Tripterygium wilfordii* Hook F), also known as Lei Gong Teng, has been adopted for generations in traditional Chinese medicine to treat inflammation. Extraction of *Tripterygium wilfordii* Hook F has been shown in animal studies to suppress both

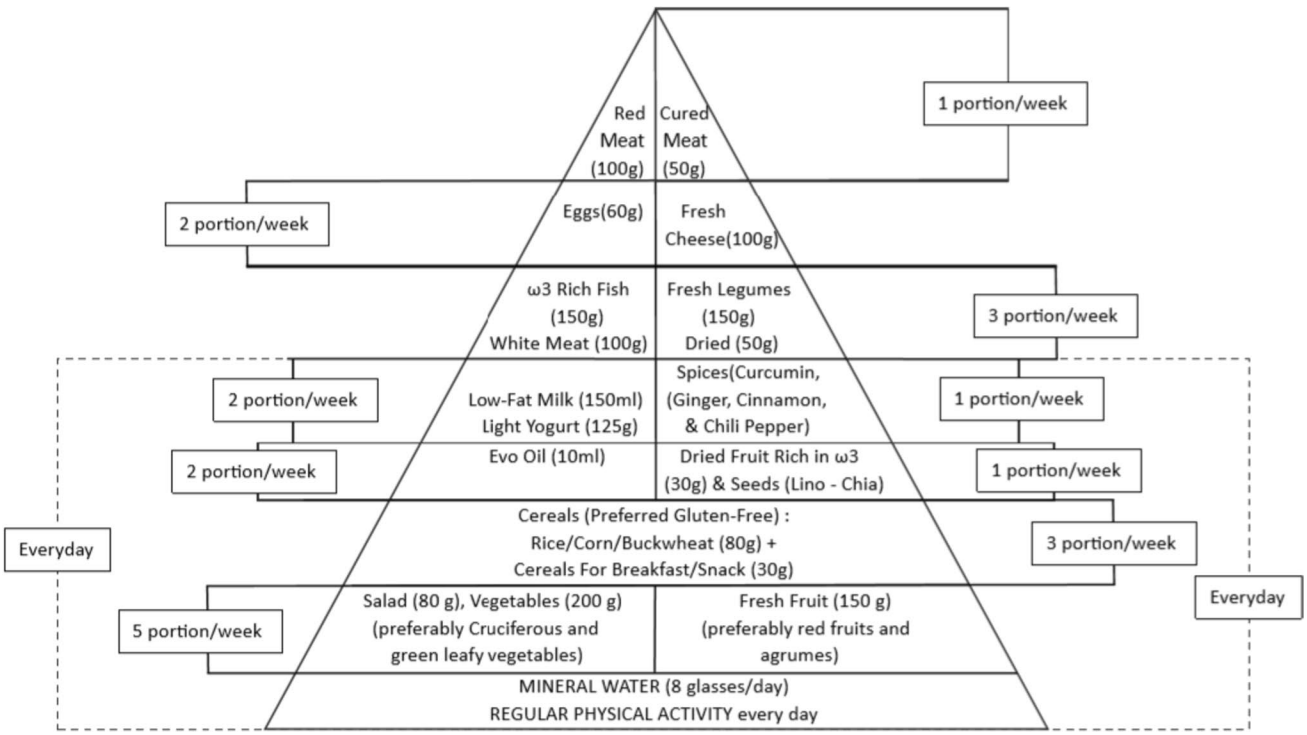


Fig. 4 A comprehensive specialized food and lifestyle pyramid for people dealing with RA involves emphasizing the consumption of anti-inflammatory foods, integrating joint-friendly exercises, prioritizing sufficient rest to promote overall health, and effectively manage RA symptoms

inflammatory and immunological reactions. In vitro studies have revealed that *Tripterygium wilfordii* Hook F components reduce immunological responses by decreasing the transcription of cytokine genes such as IL-2 and gamma interferon [97]. Thunder god vine includes various active substances with anti-inflammatory effects, including triptolide and celastrol. These substances reduce joint inflammation and pain by suppressing the activity of inflammatory agents such as cytokines and enzymes. It has the potential to modify the immune system, inhibiting hyperactive immunological responses that contribute to the development of RA. This can help to regulate an autoimmune attack on joint tissues. Thunder god vine has antioxidant activity, which means it can eliminate harmful free radicals that cause tissue damage and inflammation in RA patients [98].

Olive Oil

Olive oil contains polyphenols, including hydroxytyrosol and oleuropein, which have antioxidant properties. Antioxidants help to eliminate potentially harmful free radicals and reduce oxidative stress, two factors in RA that can lead to joint damage and inflammation. A higher risk of cardiovascular disease is associated with RA. Monounsaturated fats in olive oil and their antioxidant and anti-inflammatory compounds can positively impact cardiovascular health, which can be particularly relevant for people with RA [99].

Recommended Diets to Manage RA

A well-defined balanced diet that incorporates various antioxidant-rich foods and other healthy lifestyle habits can improve overall well-being. However, it is crucial to collaborate with your healthcare provider to establish a comprehensive strategy for effectively managing your RA [100]. The food pyramid for RA patients is given in Fig. 4.

Conclusion and Future Perspective

RA is an autoimmune disorder that affects joints, cartilage, and synovium lining of bones, finally leading to permanent damage to the bones and joints. Several treatments for RA include DMARDs, NSAIDs, glucocorticoids, and biologics. However, these therapies have significant drawbacks, including adverse effects, and biologics increase the risk for several pathogenic infections. Thus, there is a need for alternative managerial therapies which can support the RA treatment.

Herbal products can be used alongside conventional drugs as complementary therapies. Several plant-based secondary metabolites and herbal extracts have shown potential anti-RA properties. We would like to highlight some of the significant contributions of anti-RA, including vitamins, elements, secondary metabolites, and extracts that could be used as next-generation anti-RA managerial therapies. For example, vitamin C is essential for cartilage and bones and supports tissue repairs. At the same time, vitamin E possesses mild analgesic effects, and beta-carotene helps scavenge the ROS. In the element's category, selenium and zinc are part of the body's antioxidant machinery, which helps diminish free radicals and oxidative stress. Among secondary metabolites, flavonoids such as hesperidin, liquiritin, tangeretin, genistein, apigenin, quercetin, and diarylheptanoids such as curcumin reduce inflammation by acting against several anti-inflammatory pathways. In addition, peptides such as apitoxin, agkistrodon, GLPP, psalmotoxin 1, and scolopendrasin IX showed promising anti-inflammatory activity by working against several inflammatory mediators.

The pivotal focus on natural products unveils a promising avenue to elucidate the molecular intricacies by which antioxidants and plant secondary metabolites contribute to RA mitigation. THM and extracts, subjected to rigorous examination, offer valuable insight into their pharmacological efficacy and established roles in the management of RA. The above-discussed secondary metabolites, herbal extracts, elements, and peptides are based on the in vitro studies. Thus, these secondary metabolites, peptides, elements, and vitamins should be evaluated with the anti-RA drugs to confirm their therapeutic potential in the in vivo model of RA. Also, these should be assessed for their synergistic activity with the known anti-inflammatory and anti-RA drugs to develop the possible combination therapy.

Abbreviations Anti-CCP: Anti-cyclic citrullinated peptide; AP-1: Activated protein-1; B cells: Bursa-derived cells; CRP: C-reactive protein; DMARD: Disease-modifying antirheumatic drugs; ESR: Erythrocyte sedimentation rate; IκB: Inhibitor of kappa B; IL-1: Interleukin-1; IL-6: Interleukin-6; JNK: Jun N-terminal kinase; LDL: Low-density lipoprotein; LPS: Lipopolysaccharide; MAPKs: Mitogen-activated protein kinases; MMPs: Matrix metalloproteinases; mtROS: Mitochondrial reactive oxygen species; NLRP3: NOD-like receptor protein 3; NF-κB: Nuclear factor kappa B; Nrf-2: Nuclear factor erythroid 2-related factor 2; NSAIDs: Non-steroidal anti-inflammatory drugs; RF: Rheumatoid factor; ROS: Reactive oxygen species; OCP: Osteoclast precursors; RA: Rheumatoid arthritis; STAT3: Signal transducer and activator of transcription 3; T cell: Thymus cells; TAC: Total antioxidant capacity; TAK1: Transforming growth factor-β-activated kinase 1; THMs: Traditional herbal medicines; TNF: Tumor necrosis factor; VGEF: Vascular endothelial growth factor

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Author Contribution N.G, S.P., and M. wrote the main manuscript G.K. helped in data compilation as well as manuscript structuring, and A.G. was involved in conceptualization, reviewing, and editing the manuscript. All authors reviewed the manuscript.

Declarations

Conflict of Interest The authors declare no competing interests.

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