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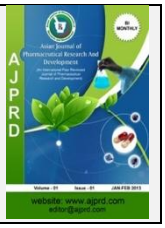

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Review Article

Natural Products and their Role in the Management of Rheumatoid arthritis: A Review of Current Evidence

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A B S T R A C T

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent joint inflammation, pain, and progressive cartilage and bone damage. Conventional pharmacological treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs), provide symptomatic relief but are associated with adverse effects and long-term management challenges. Consequently, natural products have gained attention as alternative or complementary therapeutic agents due to their anti-inflammatory and immunomodulatory properties.
Aim: This review examines the potential of natural products in managing RA by targeting key inflammatory pathways and oxidative stress, with a focus on bioactive compounds such as flavonoids, terpenoids, alkaloids, and polyphenols.
Methods: A comprehensive literature review was conducted to evaluate preclinical and clinical studies on the efficacy of natural products in RA treatment. The mechanisms of action, bioavailability concerns, and potential combination therapies were analyzed.
Results: Compounds such as curcumin, resveratrol, *Boswelliaserrata*, and ginger have demonstrated significant anti-inflammatory and immunomodulatory effects in RA models. These natural products regulate cytokine production (TNF-α, IL-6), inhibit cyclooxygenase (COX), and mitigate oxidative stress, offering multi-targeted therapeutic potential. However, challenges such as poor bioavailability and variability in composition necessitate advanced formulations and standardization.
Conclusion: Natural products provide a promising adjunct in RA management. While clinical evidence supports their efficacy, further research, large-scale clinical trials, and standardized formulations are crucial for their integration into clinical practice.
Keywords: Rheumatoid arthritis, natural products, anti-inflammatory, immunomodulation, oxidative stress, cytokine regulation

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INTRODUCTION

Rheumatoid arthritis (RA) is a prevalent long-term inflammatory and systemic autoimmune condition that primarily affects the synovial joints. It is marked by a breakdown in immune regulation of the joint synovial membrane, widespread inflammation, and the presence of autoantibodies, ultimately resulting in significant damage and destruction of cartilage and bone[1,2].Throughout the progression of RA, the synovium can become hyperplastic and invasive, leading to damage of cartilage and bone. In this process, fibroblast-like synoviocytes (FLSs), which line the joint tissues, are considered to play a central role in driving the pathological changes [4,5]. Rheumatoid

arthritis (RA) can lead to systemic symptoms like fever, anemia, osteoporosis, and muscle weakness. It can also impact multiple organs, including the skin, blood vessels, kidneys, heart, lungs, nerves, liver, intestines, and stomach, and increase the risk of cardiovascular diseases as well as cancers such as lung cancer and lymphoma[6,7]. The global incidence of RA is about 1%. Its development is influenced by a combination of genetic, environmental, and autoimmune factors. Key triggers in genetically predisposed individuals include smoking, hormones, infections, and microbiota. Currently, immunosuppressive drugs and non-steroidal anti-inflammatory drugs are widely used in treatment, but these medications come with significant side effects. To reduce the suffering of RA patients and enhance their quality of life, there is a need for new clinical treatments that are both more effective and have fewer side effects [8, 9].The mainstream medications mentioned above are commonly prescribed to patients, but they come with undesirable side effects. Additionally, some of these drugs are quite costly. Due to these drawbacks, a growing number of patients are turning to natural products to alleviate symptoms of rheumatoid arthritis (RA) and related conditions In fact, more than 36% of adults in the USA use complementary and alternative medicine (CAM) therapies [10]. Natural products have been thoroughly studied for various health issues, including cancer, infectious diseases, and autoimmune disorders. However, challenges in assessing the effectiveness of these products, along with a lack of understanding about how they work, contribute to skepticism from both the public and medical professionals. As a result, understanding the mechanism of action of natural products is a priority, as highlighted by the National Center for Complementary and Integrative Health (NCCIH) and the National Institutes of Health (NIH) in the USA. A summary of the significant validation of some common natural products in arthritis treatment is provided below [11,12].Resveratrol (RES) (3,5,4-trihydroxystilbene) is a natural antioxidant found in various plants, including Cassia obtusifolia, Veratrum nigrum, Polygonum cuspidatum, grapes, soybeans, and nuts. It offers a range of pharmacological properties and has therapeutic effects for several autoimmune diseases, including rheumatoid arthritis (RA) A clinical study [13, 14].Although the exact cause of the disease is still unknown, genetic factors contribute to some of its risks. Generally, the disease is believed to have a multifactorial origin, involving a combination of genetic, hormonal, and environmental influences. Shared epitope (SE) alleles are estimated to account for about 40% of the genetic risk [15, 16]. These alleles are linked not only to an increased susceptibility to RA but also to its severity, and they may help identify distinct genetic profiles within different RA patient groups [17].In women, hormonal factors, such as estrogen availability, play a role in the development of RA. Research has shown that an early onset of menopause, periods following menopause or childbirth, and the use of anti-estrogen treatments are linked to the onset of RA. However, the effects of systemic hormonal therapies, including contraceptives, on RA development are still uncertain [18].

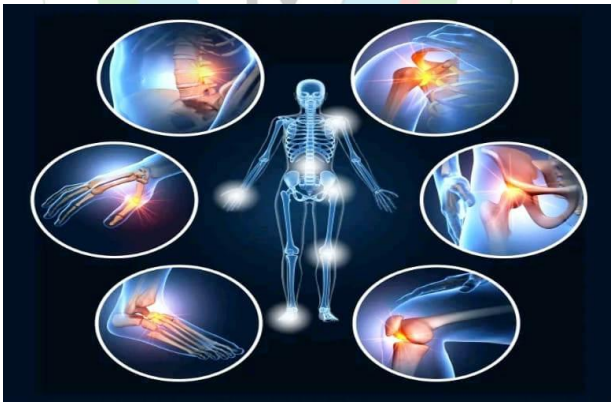


Figure 1: Various joint pain locations in the human body

Lifestyle risk factors such as smoking, secondhand smoke exposure, excessive coffee consumption, poor nutrition (low in antioxidants), and a high intake of red meat can elevate the likelihood of developing rheumatoid arthritis (RA) . It is important to explore strategies that maximize the potential combined effects of nutrition and medication to improve RA management. Hence, the purpose of this review was to evaluate the existing evidence on nutritional approaches with anti-inflammatory effects to prevent or slow the progression of RA, while also examining the benefits and risks of specific diets [19].

METHODS AND MATERIALS

This review was conducted by systematically searching scientific databases, including PubMed, Scopus, and Web of Science, for peer-reviewed articles published in the last two decades. Keywords such as "natural products," "rheumatoid arthritis," "phytochemicals," "anti-inflammatory compounds," and "immunomodulation" were used. Inclusion criteria included studies reporting pharmacological activities of natural compounds against RA, in vitro and in vivo experimental studies, and clinical trials. Data were extracted and analysed based on efficacy, safety, and mechanisms of action.

Mechanism of action against RA

Anti-inflammation and anti- oxidation

COX-2, a crucial mediator in inflammation, catalyzes the breakdown of glycerophospholipids to release arachidonic acid. This acid is then converted into prostaglandins (PGs), such as prostacyclin, thromboxane A2, PGE2, and PGD2, during the inflammatory response.PGE2, a lipid signaling molecule, plays a key role in pain and inflammation and is involved in various pathological processes. It is often overproduced in patients with rheumatoid arthritis (RA). In clinical practice, non-steroidal anti-inflammatory drugs (NSAIDs) treat RA by inhibiting COX, which reduces the production of PGE2. Selective COX-2 inhibitors, a newer class of NSAIDs, include drugs like etodolac and indomethacin.In patients with rheumatoid arthritis (RA), there is an increase in reactive oxygen species (ROS) production, lipid peroxidation, protein oxidation, and DNA damage, while the activity of the antioxidant defense system is diminished, leading to oxidative stress. Chronic oxidative stress in the synovial T-lymphocytes of RA patients is primarily caused by intracellular ROS production, especially hydrogen peroxide (H2O2). ROS are believed to contribute to the destructive pathological processes of RA. A recent study has indicated that fatty acid oxidation (FAO) metabolism plays a role in bone destruction in RA patients. Selegiline has shown potential in improving RA progression, possibly by decreasing catecholamine breakdown in the synovial fluid, thus reducing H2O2 production and inhibiting local pro-inflammatory cytokines.Given the critical roles of inflammation and oxidative stress in the development of rheumatoid arthritis (RA), researchers have concentrated on developing new drugs with strong anti-inflammatory and antioxidant properties for its treatment. Several natural medicines, including resveratrol, EGCG, hesperidin, chlorogenic acid (CA), sinomenine, andrographolide (AD), aristolochic acid (ARS), and gentiopicroside, have shown notable anti-inflammatory and antioxidant effects in managing RA[20-22].

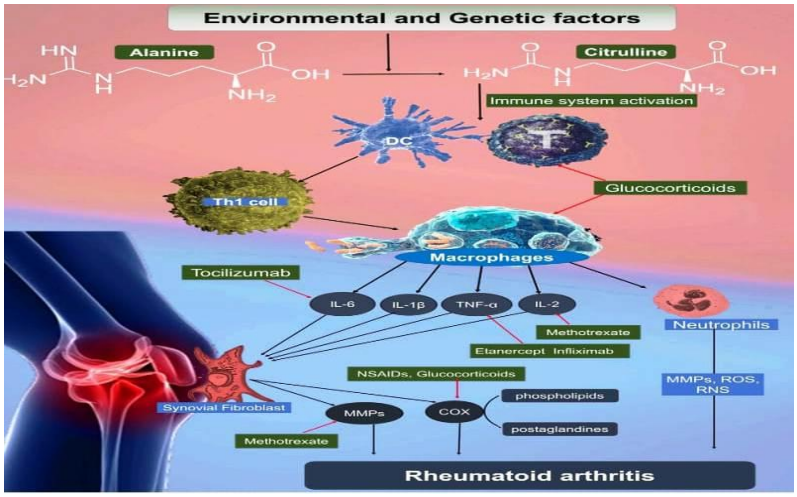
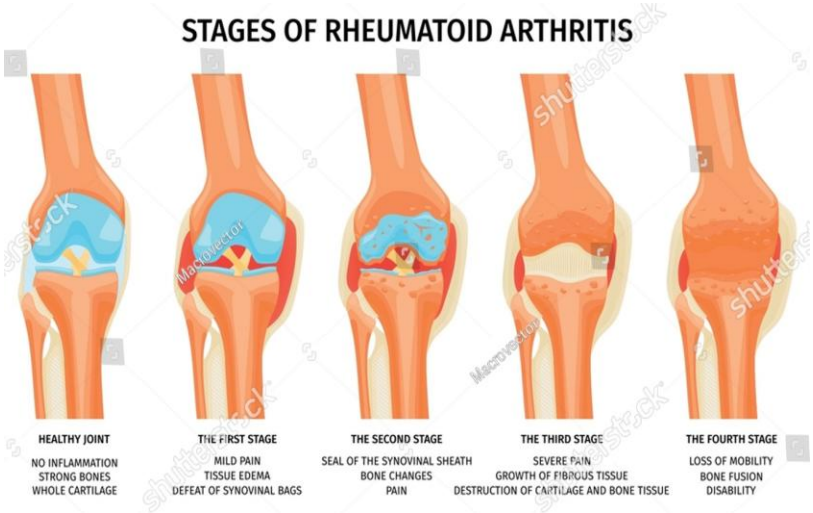


Figure 2: Mechanism of action against rheumatoid arthritis



Figur 3: Stages-rheumatoid arthritis

Immunoregulation

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by immune system dysfunction, which is a key factor in its development. Adaptive immunity plays a central role in the pathogenesis of RA. Synovial T cells contribute to the induction of antibody production and local inflammation. Specifically, CD4+ T cell subsets can differentiate to produce various pro-inflammatory cytokines and chemokines, which are involved in RA's development. The epigenetic stability of T regulatory (Treg) cells is unstable, and dysfunction of CD4+ CD25+ Foxp3+ Tregs is often seen in autoimmune diseases. These cells may also convert into pathogenic Th17 cells after repeated activation.Foxp3 is the primary regulator of immune suppression in Treg cells. One therapeutic approach for treating RA involves converting conventional Treg cells into Foxp3+ Treg cells with stable inhibitory functions, aiming to lessen inflammation associated with the transformation of Treg cells into Th17 cells. B-cell infiltration in the synovial membrane, particularly the infiltration of new B-cells into ectopic lymphoid structures, is linked to the severity of RA [23].

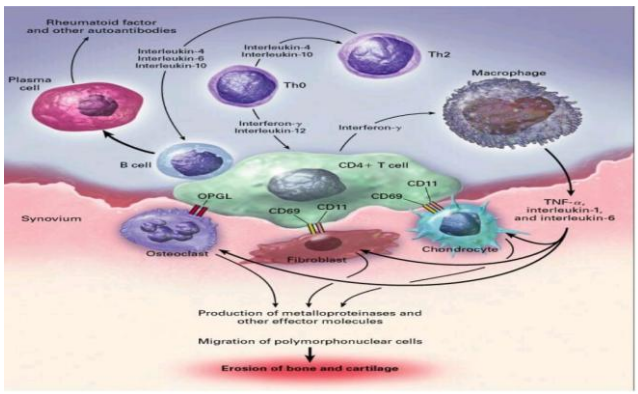


Figure 4: Immunoregulation in RA

Rheumatoid arthritis (RA) is a complex autoimmune disease influenced by genetic, environmental, and hormonal factors. While conventional treatments such as immunosuppressive and anti-inflammatory drugs help manage symptoms, they come with significant side effects and high costs, prompting interest in alternative therapies. Natural products, such as resveratrol, have shown promise in alleviating RA symptoms, though further research is needed to understand their mechanisms and efficacy. Additionally, lifestyle factors, including smoking, diet, and hormonal changes, play a crucial role in RA development and progression. Exploring integrative approaches that combine nutrition, lifestyle modifications, and pharmacological treatments could improve RA management and enhance patients' quality of life.Rheumatoid arthritis.

RESULTS AND DISCUSSION

Table.1 Medicinal Plants for used in the treatment of Rheumatoid Arthritis (RA)

S.No	Biological Name	Family	Parts of Plant Used	Phytoconstituents	Uses	Description
1	Boswelliaserrata	Burseraceae	Resin (gum)	Boswellic acids, β-boswellic acid, acetyl-β-boswellic acid	Anti-inflammatory, analgesic, immunomodulatory; used in RA	A medium-sized tree producing fragrant resin (frankincense)[24].
2	Withaniasomnifera	Solanaceae	Roots, leaves	Withanolides, alkaloids, flavonoids	Anti-inflammatory, stress reliever; reduces joint pain	A small woody shrub with yellow flowers; used in Ayurveda[25].
3	Zingiberofficinale	Zingiberaceae	Rhizome	Gingerol, shogaol, paradol	Anti-inflammatory, analgesic; reduces joint stiffness	A flowering plant with underground rhizomes, commonly used as a spice [26].
4	Curcuma longa	Zingiberaceae	Rhizome	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	Potent anti-inflammatory, antioxidant; relieves RA symptoms	A perennial herb with yellow rhizomes; widely used in traditional medicine [27].
5	Tinosporacordifolia	Menispermaceae	Stem, leaves	Alkaloids (berberine, tinosporine), glycosides, steroids	Anti-inflammatory, immunomodulatory; reduces joint pain	A climbing shrub with heart-shaped leaves; used in Ayurveda [28].
6	Ocimum sanctum	Lamiaceae	Leaves	Eugenol, ursolic acid, rosmarinic acid	Anti-inflammatory, immunomodulatory, antioxidant	A sacred basil plant used in Ayurveda for multiple medicinal properties [29].
7	Piper nigrum	Piperaceae	Fruit	Piperine, flavonoids, alkaloids	Anti-inflammatory,	A climbing vine producing black

					analgesic, enhances bioavailability of drugs	pepper, commonly used as a spice [30].
8	Emblicaofficinalis	Phyllanthaceae	Fruit	Ascorbic acid, tannins, flavonoids	Antioxidant, anti-inflammatory, boosts immunity in RA	A small tree known for its highly nutritious fruit (Indian gooseberry) [31].
9	Nigella sativa	Ranunculaceae	Seeds	Thymoquinone, alkaloids, essential oils	Anti-inflammatory, analgesic, immunomodulatory	Black cumin seeds known for their therapeutic properties.
10	Commiphoramukul	Burseraceae	Resin	Guggulsterones, flavonoids, steroids	Anti-inflammatory, reduces joint stiffness in RA	A small tree known for its resin (guggul) with medicinal properties [32].
11	Azadirachtaindica	Meliaceae	Leaves, Bark	Nimbidin, nimbin, flavonoids	Anti-inflammatory, analgesic, immunomodulatory	A fast-growing tree known as neem, widely used in traditional medicine [33].
12	Alpiniagalanga	Zingiberaceae	Rhizome	Galangin, flavonoids, essential oils	Anti-inflammatory, pain reliever for RA	A herbaceous plant known for its aromatic rhizomes used in Ayurvedic medicine [34].
13	Salix alba	Salicaceae	Bark	Salicin, flavonoids, tannins	Natural source of aspirin, anti-inflammatory, pain reliever	White willow tree, bark used for pain relief and inflammation [35].
14	Capsicum annuum	Solanaceae	Fruit	Capsaicin, flavonoids, carotenoids	Pain reliever, anti-inflammatory	Red pepper used for its capsaicin content, which helps in reducing joint pain [36].
15	Trigonellafoenum-graecum	Fabaceae	Seeds	Diosgenin, alkaloids, flavonoids	Anti-inflammatory, reduces swelling in RA	Fenugreek seeds known for their medicinal properties in Ayurveda [37].
16	Centellaasiatica	Apiaceae	Leaves	Asiaticoside, madecassoside, flavonoids	Anti-inflammatory, enhances tissue repair	A small herbaceous plant used in wound healing and joint disorders [38].
17	Glycyrrhizaglabra	Fabaceae	Root	Glycyrrhizin, flavonoids, saponins	Anti-inflammatory, immunomodulatory, reduces RA symptoms	Licorice root known for its soothing and medicinal properties [39].
18	Camellia sinensis	Theaceae	Leaves	Polyphenols, catechins, flavonoids	Antioxidant, anti-inflammatory, supports immune health in RA	Green tea plant known for its medicinal benefits [40].
19	Matricariachamomilla	Asteraceae	Flowers	Apigenin, chamazulene, flavonoids	Anti-inflammatory, pain relief in RA	Chamomile flowers commonly used in herbal medicine for inflammation reduction [41].
20	Plumbagozeylanica	Plumbaginaceae	Root	Plumbagin, flavonoids, alkaloids	Anti-inflammatory, reduces swelling and pain in RA	A medicinal shrub used in traditional Ayurvedic treatments [42].
21	Allium sativum	Amaryllidaceae	Bulb	Allicin, sulfur compounds, flavonoids	Anti-inflammatory, immunomodulatory, reduces joint pain	Garlic is widely used in herbal medicine due to its strong therapeutic properties [43].
22	Cinnamomumzeylanicum	Lauraceae	Bark	Cinnamaldehyde, eugenol, tannins	Anti-inflammatory, antioxidant, reduces joint stiffness	Cinnamon bark is commonly used in traditional medicine for its health benefits [44].
23	Hypericumperforatum	Hypericaceae	Aerial parts	Hypericin, flavonoids, tannins	Anti-inflammatory, analgesic, supports nerve health	St. John's Wort is known for its medicinal uses in pain management [45].
24	Euphorbia hirta	Euphorbiaceae	Whole plant	Flavonoids, tannins, polyphenols	Anti-inflammatory, analgesic, relieves joint swelling	A medicinal herb widely used in traditional medicine [45].
25	Symphytumofficinale	Boraginaceae	Root, leaves	Allantoin, rosmarinic acid, tannins	Anti-inflammatory, enhances tissue repair, pain relief	Comfrey has been used traditionally for wound healing and pain relief [45].
26	Urticadioica	Urticaceae	Leaves, roots	Flavonoids, lectins, sterols	Anti-inflammatory, pain reliever	Commonly known as stinging nettle, used in herbal medicine for joint pain [45].
27	Brassica nigra	Brassicaceae	Seeds	Glucosinolates, flavonoids, essential oils	Anti-inflammatory, improves circulation in joints	Black mustard seeds traditionally used for pain relief [45].
28	Tamarindusindica	Fabaceae	Pulp, seeds	Polyphenols, flavonoids,	Anti-inflammatory,	Tamarind is known for its therapeutic effects on joint

				tannins	antioxidant	inflammation [43].
29	Punicagranatum	Lythraceae	Fruit, peel	Punicalagins, ellagic acid, flavonoids	Antioxidant, reduces joint inflammation	Pomegranate is rich in polyphenols that help combat RA symptoms [42].
30	Solanumnigrum	Solanaceae	Leaves, berries	Glycoalkaloids, flavonoids, tannins	Anti-inflammatory, analgesic	Black nightshade is used in traditional medicine for joint pain relief [43].
31	Moringaoleifera	Moringaceae	Leaves, seeds	Quercetin, isothiocyanates, flavonoids	Anti-inflammatory, antioxidant	Moringa is known as a superfood with medicinal properties [46].
32	Ficusreligiosa	Moraceae	Bark, leaves	Flavonoids, tannins, saponins	Anti-inflammatory, pain reliever	Sacred fig tree used in Ayurveda for arthritis treatment [47].
33	Ricinuscommunis	Euphorbiaceae	Seeds, leaves	Ricinoleic acid, flavonoids, alkaloids	Anti-inflammatory, reduces joint swelling	Castor oil plant used traditionally for joint pain relief [48].
34	Adhatodavasica	Acanthaceae	Leaves	Vasicine, flavonoids, alkaloids	Anti-inflammatory, analgesic	Malabar nut plant used in Ayurveda for various medicinal purposes [49].
35	Menthapiperita	Lamiaceae	Leaves	Menthol, flavonoids, polyphenols	Pain reliever, cooling effect on joints	Peppermint used in herbal medicine for pain management [50].
36	Peganumharmala	Nitrariaceae	Seeds, roots	Harmine, alkaloids, flavonoids	Anti-inflammatory, analgesic	Syrian rue plant used in traditional medicine for pain relief [51].
37	Tribulusterrestris	Zygophyllaceae	Fruits, roots	Saponins, flavonoids, alkaloids	Anti-inflammatory, supports joint health	Puncture vine is used in Ayurveda for various medicinal purposes [52].
38	Aloe vera	Asphodelaceae	Leaves	Aloin, polysaccharides, flavonoids	Anti-inflammatory, soothing effect on joints	Aloe vera is widely used for its medicinal and therapeutic benefits [53].
39	Cissusquadrangularis	Vitaceae	Stem	Ascorbic acid, carotenoids, flavonoids	Anti-inflammatory, bone strengthening	Hadjod plant used in Ayurveda for joint and bone health [54].
40	Smilax china	Smilacaceae	Rhizome, roots	Saponins, flavonoids, tannins	Anti-inflammatory, detoxifying	Chinese smilax is used in traditional medicine for arthritis relief [55].
41	Silybummarianum	Asteraceae	Seeds	Silymarin, flavonoids, polyphenols	Anti-inflammatory, antioxidant	Milk thistle is widely used for its liver and joint benefits [56].
42	Artemisia annua	Asteraceae	Leaves, stems	Artemisinin, flavonoids, alkaloids	Anti-inflammatory, immunomodulatory	Sweet wormwood known for its medicinal benefits [57].
43	Berberisaristata	Berberidaceae	Stem, roots	Berberine, flavonoids, alkaloids	Anti-inflammatory, pain reliever	Tree turmeric used in Ayurveda for its medicinal properties [58].
44	Justiciagendarussa	Acanthaceae	Leaves, stems	Flavonoids, alkaloids, lignans	Anti-inflammatory, supports joint health	Used in traditional medicine for pain management [59].
45	Leucasaspera	Lamiaceae	Leaves, flowers	Flavonoids, tannins, alkaloids	Anti-inflammatory, relieves joint pain	A medicinal herb commonly used in Ayurveda [60].
46	Phyllanthusamarus	Phyllanthaceae	Whole plant	Lignans, flavonoids, tannins	Anti-inflammatory, antioxidant	Used in herbal medicine for liver and joint health [61].
47	Plectranthusamboinicus	Lamiaceae	Leaves	Thymol, carvacrol, flavonoids	Anti-inflammatory, pain reliever	Indian borage is used traditionally for arthritis relief [62].
48	Ecliptaprostrata	Asteraceae	Whole plant	Wedelolactone, flavonoids, polyphenols	Anti-inflammatory, strengthens connective tissue	Used in Ayurveda for joint and bone health [63].
49	Abutilon indicum	Malvaceae	Leaves, roots	Alkaloids, flavonoids, tannins	Anti-inflammatory, pain reliever	Commonly used in Ayurveda for arthritis treatment [64].
50	Clerodendrumserratum	Lamiaceae	Leaves, roots	Flavonoids, alkaloids, terpenoids	Anti-inflammatory, relieves swelling	Traditional medicine herb used for joint pain [65].
51	Vitexnegundo	Lamiaceae	Leaves, bark	Flavonoids, alkaloids, terpenoids	Anti-inflammatory, analgesic	Used in Ayurveda for arthritis and joint pain relief [66].
52	Plumbagozeylanica	Plumbaginaceae	Roots, leaves	Plumbagin, flavonoids, tannins	Anti-inflammatory, pain reliever	Traditional medicine plant for joint pain management [67].
53	Costusspeciosus	Costaceae	Rhizome, leaves	Diosgenin, flavonoids, tannins	Anti-inflammatory, antioxidant	Used in herbal medicine for inflammation reduction [68].

CONCLUSION

Rheumatoid arthritis (RA) is a complex autoimmune disorder influenced by genetic, environmental, and hormonal factors. While conventional treatments, including immunosuppressive and anti-inflammatory drugs, remain the primary approach, their adverse effects and financial burden highlight the need for alternative therapeutic options. Natural products have gained significant attention for their potential in RA management, with compounds like resveratrol demonstrating promising anti-inflammatory and immunomodulatory effects. However, further research is needed to fully elucidate their mechanisms, optimize formulations, and validate clinical efficacy. Additionally, lifestyle factors such as diet, smoking, and hormonal fluctuations play a critical role in disease onset and progression. Integrating natural products with lifestyle modifications and conventional therapies may provide a holistic and more sustainable strategy for RA management, improving patient outcomes and quality of life.

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CONFLICT OF INTERESTS

We have No conflict interest.

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