



REVIEW ARTICLE

# Herbal Allies for Rheumatoid Arthritis: A Comprehensive Review of Natural Products

Ankita Singh<sup>1,2</sup>, Madhu Kaushik<sup>1</sup>, Swati Sinha<sup>1</sup>, Ravindra Kumar Kachhap Oraon<sup>1</sup>, Narotam Sharma<sup>2</sup> and Indra Rautela<sup>1\*</sup>

<sup>1</sup>Department of Biotechnology, School of Applied and Life Sciences (SALS), Uttarakhand University, Dehradun-248007, Uttarakhand, India

<sup>2</sup>DNA Labs- A Centre for Applied Sciences, Dehradun-248007, Uttarakhand, India

\*Email: [rautela.indra7@gmail.com](mailto:rautela.indra7@gmail.com)



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## Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting primarily the joints, producing discomfort, inflammation, and potentially damaging joint destruction. Rheumatoid arthritis affects people all around the world, and its prevalence and impact differ by place. The World Health Organisation (WHO) estimates that 0.5% to 1% of the global population has rheumatoid arthritis. To decrease the progression of rheumatoid arthritis, disease-modifying anti-rheumatic medications (DMARDs) such as methotrexate and sulfasalazine are used. TNF inhibitors and IL-6 inhibitors are two examples of biologic DMARDs that target specific immune system components. Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics help manage pain and inflammation while corticosteroids provide short-term relief during flares. Treatment strategies are tailored to the individual, and talking with a healthcare expert is essential for effective management. Herbal therapies are regarded to offer an advantage over synthetic pharmaceuticals for the treatment of rheumatoid arthritis due to their natural approach, potential symptom relief, holistic approach to health, and individualised therapy possibilities. However, scientific data supporting their effectiveness is sparse and variable, and their quality and safety can vary. Before adopting herbal therapies as part of a treatment plan, it is critical to check with a healthcare expert. Because of their natural chemicals with anti-inflammatory and analgesic characteristics, medicinal herbs may aid rheumatoid arthritis. However, further research is required to determine their efficacy, safety, and appropriate application.

## Keywords

Rheumatoid Arthritis, Natural products, Photoactive compounds, anti-inflammatory and anti-arthritis effects

## Introduction

Rheumatoid Arthritis (RA) is most prevalent in European, Asian, North American, and South American countries and less abundant in China, France, Italy, Serbia, and the US population (1). It is depicted by inflammation of the synovial joint lining, leading to pain, swelling, stiffness, and eventually joint destruction (2-4). It is estimated that 0.5-1% of adults worldwide have RA, with a higher prevalence in women and increasing incidence with age (5, 6). Rheumatoid Arthritis can also affect other organs, such as the lungs, heart, and blood vessels, and it has a considerable effect on the patient's complete health and quality of life (6-8). Preventing or minimising joint deterioration and enhancing quality of life need early diagnosis and treatment (2-4, 9).

The American College of Rheumatology proposed a "treat-to-target" approach to RA treatment in 2015, in which therapy is targeted to achieve low disease activity with disease-modifying anti-rheumatic medications (DMARDs) or additional biologic medicines (10). This strategy has been found to enhance outcomes for RA patients, including less disease activity, less joint damage, and greater physical function (11). The DAS28 is a regularly used RA disease activity metric that takes into account the number of sore, swollen joints, ESR, and the patient's overall assessment of disease activity. A DAS28 value of 3.2 suggests mild disease activity or remission, whereas a score of greater than 5.1 indicates significant disease activity (12). While there is no cure for RA, early diagnosis and treatment can help slow disease progression and improve patient outcomes. In addition to pharmacologic therapies, non-pharmacologic approaches such as exercise, physical therapy, and dietary modifications may also be beneficial for managing RA symptoms and improving quality of life. On going research into the pathogenesis of RA and the development of new treatment strategies offer hope for improved outcomes for patients with this chronic condition. The main target of RA therapy is to reduce inflammation and pain, preserve joint function, and improve the patient's overall quality of life (2-4).

Nonsteroidal anti-inflammatory drugs (NSAIDs) including ibuprofen and naproxen are routinely used to treat inflammation as well as pain in RA (2, 10). Methotrexate and sulfasalazine are two disease-modifying anti-rheumatic medications that are routinely administered to delay the course of the disease. Biologic DMARDs are a group of drugs which includes inhibitors of tumor necrosis factor and interleukin-6 to reduce inflammation and slow joint damage in RA (2, 10). Sometimes a combination of these treatments may be necessary to achieve optimal results. The use of natural products in traditional medicine has been gaining attention due to their potential health benefits. The current study highlights some common names, plant families, and the parts used by plants along with their other photoactive compounds. *Zingiber officinale* (Ginger) belongs to the Zingiberaceae family, is commonly used for RA due to its diarylheptanoid, Yakuchinone A, and Proanthocyanidin content (13). *Vitis vinifera* (European wine grape) roots contain resveratrol and have been used for various health benefits (14). Guggul, derived from the gum resin of *Commiphora wightii*, contains lysosomal enzymes and is known for its anti-inflammatory effects (15). *Withania somnifera* powder contains withanolide and has been found to suppress the nuclear factor- $\kappa$ B activation (16). Boswellic acid, present in *Boswellia serrata* (Indian frankincense), has been shown to potentiate apoptosis, inhibit invasion, and abolish osteoclast genesis (17). Chinese wolfsbane, or *Aconitum Carmichaelii*, contains alkaloids that can have effects on the central nervous system (18). Cinnamon bark (*Cinnamomum cassia*) contains terpenoids, phenylpropanoids, and has been used for various medicinal purposes (19).

## Methodology

### Search strategy

We accomplished extensive searches across multiple databases, including PubMed, Web of Science, Scopus, EMBASE, China Scientific Journal Database (VIP), and Wan Fang Database. In order to obtain grey literature, we expanded our search to include PubMed Central and Open Grey. Notably, our search was not constrained by language or publication date.

### Study selection criteria

We chose articles that fulfilled the following criteria:

1. The investigation of herbal remedies as a therapy technique for rheumatoid arthritis should be the focus of the study.
2. Studies comparing the efficacy of herbal medicines to other treatment choices such as disease-modifying anti-rheumatic drugs (DMARDs), TNF inhibitors, IL-6 inhibitors, NSAIDs, analgesics, and corticosteroids may be included.
3. The efficacy, safety, symptom relief, and holistic health approach of herbal therapy for rheumatoid arthritis should be evaluated in the study.

Studies addressing the need for additional research on the efficacy, safety, and proper use of herbal medicines in the treatment of rheumatoid arthritis will also be useful.

### Inclusion criteria

The evaluation will investigate the use of natural goods, notably herbal remedies, as interventions in the management or treatment of Rheumatoid Arthritis. Only studies involving human subjects, of any age or gender, will be accepted. The selected research will include both clinical trials and observational studies. The evaluation will look at outcomes like efficacy, safety, symptom alleviation, disease progression, and any side effects connected with the use of herbal allies for Rheumatoid Arthritis. Herbal allies ranging from single herbs to herbal combinations will be considered. The complete review seeks to provide significant insights into the potential benefits and limitations of herbal allies in controlling Rheumatoid Arthritis, adding to a greater knowledge of their function in the treatment of this condition by adhering to these inclusion criteria.

### Exclusion criteria

During the complete study of "Herbal Allies for Rheumatoid Arthritis: A Comprehensive Review of Natural Products," various exclusion criteria will be used to refine the selection process. To retain the review's relevance and application, studies that do not clearly focus on Rheumatoid Arthritis as the target condition will be eliminated. Non-human studies, including animal and in vitro experiments, will also be eliminated because they may not translate directly to human applications. To ensure originality and minimise redundant data, review articles, meta-analyses, systematic reviews, case reports, and case series will be excluded. Non-interventional research, such as those that do not involve the use of

herbal allies as Rheumatoid Arthritis therapies will be excluded from the review. Furthermore, studies including synthetic medications or non-herbal therapies will be avoided in order to keep the focus on natural items. The review will prioritise studies with sufficient data, avoiding those with incomplete outcome reporting. Unpublished studies, conference abstracts, and posters will also be removed to ensure the availability of complete and detailed data. Studies having a significant risk of bias or methodological flaws that may jeopardise the trustworthiness of the results will also be rejected. Using these exclusion criteria, the thorough review seeks to provide a solid and trustworthy analysis of relevant studies on herbal allies and their potential efficacy in Rheumatoid Arthritis therapy.

### Keyword using for search

Specific keywords were utilised to discover relevant literature during the search for the full review. The major keywords were "herbal allies," "natural products," "Rheumatoid Arthritis," "comprehensive review," and variations of these terms, such as "herbal remedies," "herbal therapies," "herbal interventions," "RA," "natural remedies," and "herbal medicine." Additional terms linked to Rheumatoid Arthritis and herbal treatments will be included, such as "herbal supplements," "herbal formulations," "traditional medicine," "phytotherapy," and "herbal extracts." The combination of these key terms will aid in the identification of relevant research on the use of herbal allies and natural goods in the management and treatment of Rheumatoid Arthritis.

## Results

### The Role of Natural Products in the Management of Rheumatoid Arthritis

RA can strike at any age, but it most typically affects people between the ages of 30 and 50. Women are more prone than men to acquire RA, with a female-to-male ratio of roughly 3:1 (2, 3). Rheumatoid Arthritis (RA) is a progressive disease that, if left untreated, can lead to disability and shortened life expectancy. Fig. 1 depicts the progression of RA (2, 3, 8). Early detection and therapy are critical for preventing or minimising joint deterioration and increasing life value (2-4, 9).

The ethnic medicinal system using various ayurvedic plants is a popular practice in India. The term Vata is used to denote rheumatism. As in RA joints are affected, it becomes sandhivata in which sandhi means joints (20). The plants with potential immunomodulatory, anti-inflammatory, and eventually, anti-arthritic properties are used for managing RA (Table 1).

Some methods for treating RA are considered unconventional as Ayurveda states them to be effective but there is not enough scientific evidence to support such statements. One of such method is *svedna* which includes sweating or heating. Another most commonly ayurvedic practice is *snehana* which means lubrication (28). The lubrication is commonly called 'ayurvedic massage' in which selected oils to reduce fatigue and pain by a specific massaging technique. It helps in stimulating the nervous system and pressure points are treated (20). These are not

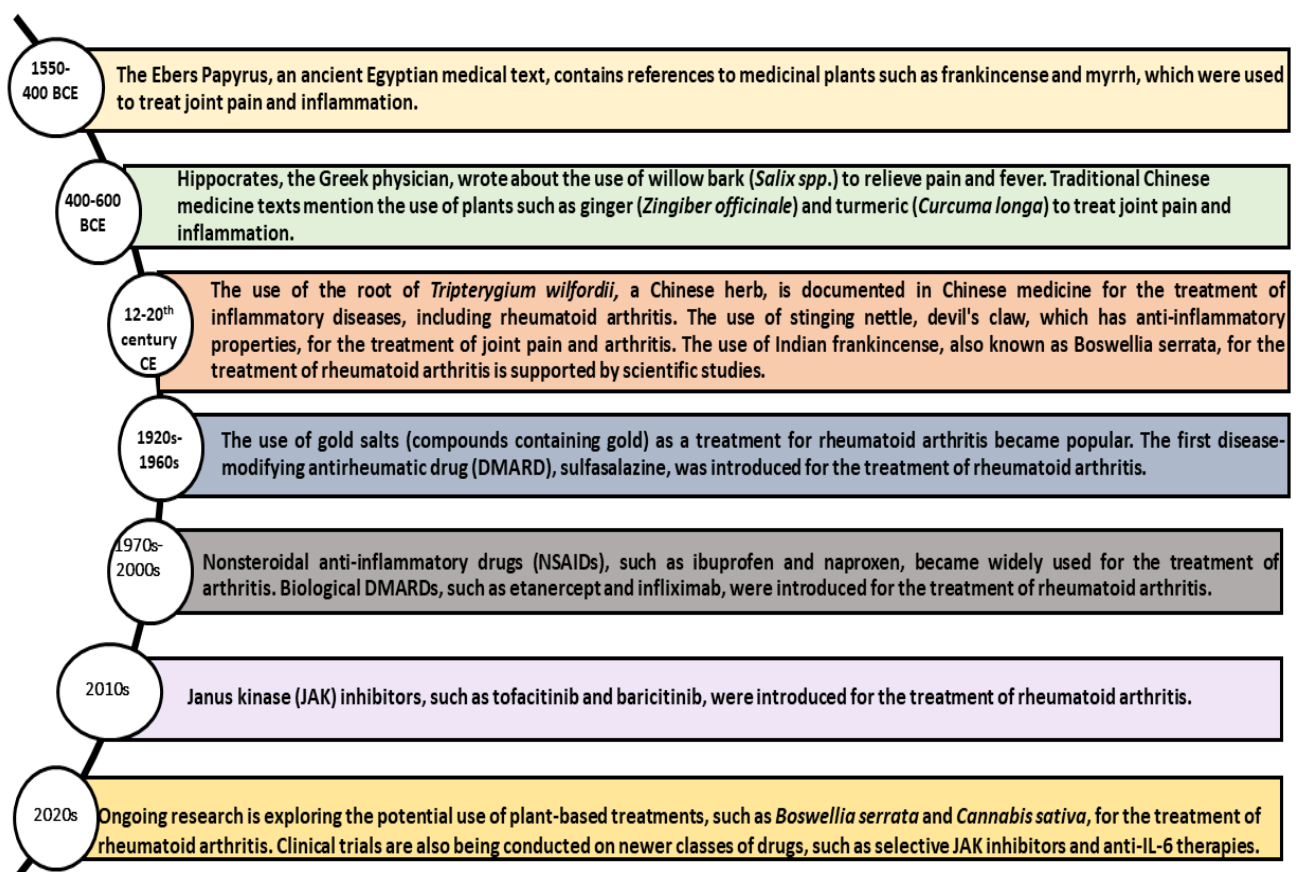


Fig. 1. Timeline chart on Rheumatoid arthritis treatments and immunological updates.

**Table 1.** Plants mentioned in classical Indian Texts for management of RA.

| S. No. | Name of the plant          | Regional name (language) | Text mentioned (Ayurveda/siddha)       | Pharmacological action (only wrt RA or inflammation)   | Reference |
|--------|----------------------------|--------------------------|--|--|-----------|
| 1.     | <i>Boswellia serrata</i>   | Salai guggul (Hindi)     | Sushrita Samhita texts, Chakra Samhita | Reducing joint pain, irritation, and stiffness, inhibit pro-inflammatory cytokines                   | (21)      |
| 2.     | <i>Allium sativum</i>      | Vellulli (Malayalam)     | Sushrita Samhita texts, Chakra Samhita | Reduce fatigue, improvements of peripheral circulation, anti-oxidative and anti-inflammatory effects | (22, 23)  |
| 3.     | <i>Zingiber officinale</i> | Adraka (Sanskrit)        | Sushrita Samhita texts, Chakra Samhita | Target NF-κB and MAPK signalling   | (24-26)   |
| 4.     | <i>Ricinus communis</i>    | Arandi Kaa Tel (Hindi)   | Sushrita Samhita texts, Chakra Samhita | Anti-inflammatory, antithrombic and anti-atherogenic,  | (27)      |
| 5.     | <i>Withania somnifera</i>  | Ashwagandha (Bengali)    | Sushrita Samhita texts, Chakra Samhita | Anti-inflammatory and immune-modulatory effects  | (16)      |

standard practices, but many households follow them as a custom. Certain Ayurvedic formulations are popular which are believed to have medicinal properties in treating RA.

They are believed to increase body's resistance, delay aging, enhancing intellect and strength. Bhasma is prepared by mixing guggul with non-toxic mineral like gold, silver and iron. It is believed to have healing properties. Different Rasayanas are also prepared by missing plant herbs in different proportions (Table 2). These Ayurvedic treatments effectively induce immunological response in the human body. The cell signalling like NF-κB, ERK, p38 MAP kinase, and JNK are targeted. The B and T cells are proliferated, and cytokines are released in response to the disease (29).

Plants have been used in traditional medicine for their medicinal properties for centuries (Fig. 2, 3). These plants contain bioactive compounds that are beneficial for human health. Some medicinal plants along with their bioactive compounds are incorporated in Table 3.

Cinnamon (*Cinnamomum cassia*): Cinnamon is a spice obtained from the inner bark of *Cinnamomum cassia*, a tree native to Southeast Asia. The bark is rich in gallic acid, polyphenols, terpenoids, phenylpropanoids, and glycosides possess anti-inflammatory and antioxidant properties. Cinnamon has been shown to ameliorate the symptoms of RA by reducing inflammation and oxidative stress (19, 30).

Thunder God Vine (*Tripterygium wilfordii*): It has demonstrated promising potential as a natural resource for treatment of RA due to its anti-inflammatory, immunomodulatory, and analgesic effects. The active

compounds in *T. wilfordii*, such as triptolide and celastrol, have been shown to effectively alleviate rheumatoid arthritis symptoms and improve joint function in both preclinical and clinical studies. Its compounds are warranted, but this plant has shown great promise as a potential alternative or complementary therapy for rheumatoid arthritis patients (19, 31).

Ginger (*Zingiber officinale*): has been traditionally used for its anti-inflammatory and analgesic properties. Recent studies have reported that ginger, ginger oil, and its bioactive compounds such as diarylheptanoid, Yakuchinone A, terpenes, and Proanthocyanidin have significant anti-arthritis properties over animal models for rheumatoid arthritis. Moreover, clinical studies have also demonstrated the efficacy of ginger in reducing joint pain, swelling, and stiffness in rheumatoid arthritis patients. Ginger inhibits various inflammatory pathways directly involved with rheumatoid arthritis, such as the NF-κB and MAPK signaling pathways, thus providing a potential therapeutic option for managing the symptoms of rheumatoid arthritis. A study found that taking ginger supplements for 3 months significantly reduced levels of certain inflammatory markers in patients with RA (32-34).

Purple willow (*Salix purpurea*): It is the potential as a natural resource for the treatment of arthritis and rheumatism due to its anti-inflammatory, analgesic, and antioxidant properties. The active compounds in purple willow, such as salicin and salicylic acid, have been shown to effectively alleviate arthritis symptoms and improve joint function in both preclinical and clinical studies. Purple willow has shown promising potential as a natural

**Table 1.** Plants mentioned in classical Indian Texts for management of RA.

| S. No. | Name of the formulation | Name of the plant involved in formulation | Text mentioned (Ayurveda/siddha)       | Pharmacological action                           | Reference |
|--------|-------------------------|---|--|--|-----------|
| 1.     | Rasayana                | Ashwagandha, Ricinus communis, guggul     | Sushrita Samhita texts, Chakra Samhita | Targeting NF-κB, ERK, p38 MAP kinase, and JNK    | (29)      |
| 2.     | Bhasma                  | Guggul                                    | Chakra Samhita                         | Enhance Th1 cytokine, B and T cell proliferation | (29)      |

alternative or complementary therapy for arthritis and rheumatism patients, but further research is needed to fully understand its safety and efficacy (18).

**Black nightshade (*Solanum nigrum* Linn):** A medicinal plant that has shown promising potential in the treatment of various diseases, including rheumatoid arthritis, due to its anti-inflammatory and analgesic properties. The active compounds in *S. nigrum*, such as solasodine and solanine, have been shown to possess anti-inflammatory, antioxidant, and immunomodulatory effects, which may help alleviate symptoms of rheumatoid arthritis (35).

**European Wine Grape (*Vitis vinifera*):** The ultrasonic extraction of *Vitis vinifera* roots contains resveratrol, a polyphenolic compound known for its antioxidant, anti-cancer, and anti-inflammatory properties. Resveratrol has shown promising results in ameliorating the symptoms of rheumatoid arthritis by suppressing the production of inflammatory cytokines and regulating immune response (14, 36).

**Guggul (*Commiphora wightii*):** Guggul, also known as *Commiphora wightii*, is a tree that produces a resinous gum with anti-inflammatory properties. The gum resin contains a lysosomal enzyme that possesses anti-inflammatory properties, making it an efficient remedy for RA and other chronic diseases (15).

**Ashwagandha (*Withania somnifera*):** Ashwagandha is a popular herb in Ayurvedic medicine that has been traditionally used to treat a variety of ailments, including rheumatoid arthritis. The root powder of the plant contains the lysosomal enzyme, Withanolide, which has been shown to possess anti-inflammatory and immunomodulatory effects, making it a promising treatment option for rheumatoid arthritis (16, 37).

**Indian Frankincense (*Boswellia serrata*):** Indian Frankincense, also known as *Boswellia serrata*, is a tree that produces a resinous extract with anti-inflammatory properties. The extract contains boswellic acids, which have been shown to possess potent anti-inflammatory effects and inhibit the synthesis of pro-inflammatory cytokines. *Boswellia serrata* extract has also shown promising results in reducing joint discomfort and irritation in rheumatoid arthritis patients (17, 38, 39).

**Chinese Wolfsbane (*Aconitum Carmichaelii*):** *Aconitum Carmichaelii*, commonly known as Chinese wolfsbane, is a poisonous plant traditionally used in Chinese medicine to treat rheumatoid arthritis. The plant contains alkaloids that have been shown to possess anti-inflammatory and analgesic effects. However, caution should be exercised when using this plant, as it can be toxic in high doses (18).

**Turmeric (*Curcuma longa*)** is a popular herbal ally for RA and has been found to have anti-inflammatory properties (7). Turmeric contains a compound called curcumin, which has been shown to inhibit inflammatory mediators and reduce oxidative stress in the body (8, 40).

*Boswellia serrata* is another herb that has been traditionally used to treat inflammatory conditions, including RA. The resin of this plant contains compounds that have been shown to have anti-inflammatory and analgesic properties. Some studies have found that its supplements may be effective in reducing joint pain and stiffness in patients with RA (41). Devil's claw (*Harpagophytum procumbens*) is another herb that may be beneficial for RA. Devil's claw contains compounds that have anti-inflammatory and analgesic properties and has been found to reduce pain and improve mobility in patients with RA (8, 42).



**Fig. 2.** Some plants helpful in the treatment of Rheumatoid arthritis.



**Fig. 3.** Medicinal plants and their phytoactive compounds, useful for the treatment of Rheumatoid Arthritis.

**Table 3.** Some medicinal plants and their active compounds utilized for RA treatment.

| S. No | Common Name         | Plant species                       | Part used     | Major Phyto active compound   | References   |
|-------|---------------------|-------------------------------------|---------------|---|--------------|
| 1     | Ginger              | <i>Zingiber officinale</i>          | Rhizomes      | Diarylheptanoid, Yakuchinone A, Proanthocyanidin, Gingerol and terpenes | (13, 33, 34) |
| 2     | European wine Grape | <i>Vitis vinifera</i>               | Roots         | Resveratrol   | (14, 36)     |
| 3     | Guggul              | <i>Commiphora mukul</i>             | Trunk         | Lysosomal enzyme  | (15)         |
| 4     | Ashwagandha         | <i>Withania somnifera</i>           | Root          | Withanolide   | (16, 37)     |
| 5     | Indian frankincense | <i>Boswellia serrata</i>            | Trunk         | Boswellic acid  | (41, 43)     |
| 6     | Chinese wolfsbane   | <i>Aconitum carmechaeli Debeaux</i> | Tuberous root | Alkaloids   | (18)         |
| 7     | Cinnamon            | <i>Cinnamomum cassia Presl</i>      | Bark          | Terpenoid, Phenylpropanoids, glycosides                                 | (19, 30)     |
| 8     | Thunder God Vine    | <i>Tripterygium wilfordii</i>       | Roots         | Triptolide  | (31, 44)     |
| 9     | White Willow        | <i>Salix alba</i>                   | Leaves bark   | Salicin   | (17)         |
| 10    | Black Nightshade    | <i>Solanum nigrum</i>               | Seeds         | Solanine  | (35)         |
| 11    | Devil's Claw        | <i>Harpagophytum procumbens</i>     | Tubers Roots  | Harpagoside   | (42, 45)     |
| 12    | Turmeric            | <i>Curcuma longa</i>                | Rhizomes      | Curcumin  | (7, 40)      |
| 13    | Aloe                | <i>Aloe vera</i>                    | Leaves        | Aloin   | (46)         |
| 14    | Cat's Claw          | <i>Uncaria tomentosa</i>            | Bark          | Uncarinic acid  | (38)         |
| 15    | Ashwagandha         | <i>Withania somnifera</i>           | Roots         | Withanolide A   | (39)         |
| 16    | Fennel              | <i>Foeniculum vulgare</i>           | Seeds         | Anethole  | (8)          |
| 17    | Marijuana           | <i>Cannabis sativa</i>              | Leaves        | Cannabidiol   | (47)         |

The crude *Aloe vera* gel shows the potential option for rheumatoid arthritis based on its anti-inflammatory and immunomodulatory effects, as observed in both human and rat clinical parameters (46). Various active compounds were reported in Cat's claw (*Uncaria tomentosa*), including alkaloids, flavonoids, and tannins, and their potential benefits in treating various health conditions such as inflammation, arthritis, cancer, viral infections, and improving immune function (38). Cat's claw has a broad range of therapeutic applications and has been traditionally used for centuries in Peruvian folk medicine (38).

Fennel (*Foeniculum vulgare*) has been traditionally used for various medicinal purposes such as digestive and respiratory disorders, menstrual and lactation problems, and as a galactagogue. The major phytochemicals present in Fennel are volatile oils, flavonoids, coumarins, and phenolic acids. The volatile oil is the main bioactive constituent and contains mainly anethole, fenchone, and estragole (8). Fennel exhibits various pharmacological activities such as antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anticancer, and neuroprotective activities. It also shows beneficial effects on the digestive and respiratory systems and has estrogenic and lactogenic effects (8).

Marijuana (*Cannabis sativa* L.) is a versatile medicinal plant that has been used for various purposes throughout history. Its therapeutic potential has been demonstrated through numerous scientific studies, and it continues to gain acceptance as a legitimate form of medicine. With the growing interest in cannabis research, there is a need for further exploration of its potential applications, as well as continued efforts to address regulatory and legal issues surrounding its use (47-49). Table 4 shows various phytochemical compound and their regulatory pathways related to inflammation. Phytochemical compounds are naturally occurring plant-based compounds that possess therapeutic properties, including anti-inflammatory effects. The first compound listed is a mixture of several phytochemicals, including diarylheptanoid, yakuchinone A, proanthocyanidin, gingerol, and terpenes. These compounds have been found to inhibit COX-1 and COX-2, which are enzymes that play a key role in the formation of prostaglandins and suppress leukotrienes, which are inflammatory mediators (50).

Resveratrol, another compound listed, activates the SIRT1 pathway. SIRT1 is a protein that has been associated with many beneficial effects, including the modulation of inflammation (51). Guggul sterol inhibits pro-inflammatory signals and NF-kb (Transcription factor), which plays a central role in regulating the immune response to infection and inflammation (52). Withanolide docks the COX-2 active sites, thereby preventing the formation of inflammatory mediators (53). Boswellic acid inhibits 5-LOX formation, which is another enzyme involved in the formation of inflammatory mediators (52).

Fuzi lipid-soluble alkaloids lower the expression of TNF- $\alpha$ , IL-6, COX-2, and NF-kbsignaling pathways, which

are all involved in inflammation (54). Terpenoids, phenylpropanoids, and glycosides inhibit mPGES-1, an enzyme that produces prostaglandin E2, a pro-inflammatory mediator (55). Salicin modulates the Nrf2-HO-1-ROS pathway, which is involved in oxidative stress and inflammation (56). Solanine suppresses the expression of iNOS, COX2, and PGE2, which are all involved in the inflammatory response (57). Harpagoside decreases the expression of TNF- $\alpha$  and ICAM-1 mRNA, which is involved in inflammation and the immune response (58). Curcumin has been found to alleviate CIA-mediated inflammation and synovial hyperplasia (59). Aloin inhibits receptor activators of nuclear factor kappa-, which have an impact on bone resorption and inflammation (60). Cannabidiol inhibits inflammatory mediators (61). Puncalagin reduces TNF-alpha and other pro-inflammatory compounds (62). Cinnamaldehyde inhibits the PI3/AKT signalling pathway, which is involved in inflammation and cell growth (63).

## Discussion

The therapy of rheumatoid arthritis (RHA) with several phytochemicals and medicinal plants has shown encouraging outcomes in recent years. Additionally, the most popular forms of herbal and nutritional management do not display the same levels of toxicity as traditional therapy methods. A significant portion of current research is focused on the identification, isolation, and characterization of active principles from crude extracts of well-known medicinal herbs, frequently overlooking the possibility that the potent synergism of multiple constituents present in the crude drug may prove more potent and effective than any single purified compound and may help to mitigate the toxic effects of individual

**Table 4.** Phyto active compounds and their working pathway related to Rheumatoid Arthritis

| Sl.No. | Phytochemical compound  | Regulatory pathway   | Reference |
|--------|---|--|-----------|
| 1      | Diarylheptanoid,<br>Yakuchinone A,<br>Proanthocyanidin, Gingerol and terpenes | Inhibits COX-1, COX-2 and suppress leukotrienes                                  | (50)      |
| 2      | Resveratrol   | Activation of SIRT1 pathway  | (51)      |
| 3      | Guggulsterol  | Inhibit pro-inflammatory signals and NF-Kb(Transcription factor)                 | (52)      |
| 4      | Withanolide   | Dock the COX-2 active sites  | (53)      |
| 5      | Boswellic acid  | Inhibit 5-LOX formation  | (52)      |
| 6      | Fuzi lipid soluble alkaloids  | Lower the expression of TNF- $\alpha$ , IL-6, COX-2 and NF-kb signalling pathway | (54)      |
| 7      | Terpenoid,<br>Phenylpropanoids, glycosides                                    | mPGES-1 inhibitor  | (55)      |
| 8      | Salicin   | Nrf2-HO-1-ROS pathway modulation   | (56)      |
| 9      | Solanine  | Suppression of iNOS, COX2 and PGE <sub>2</sub>                                   | (57)      |
| 10     | Harpagoside   | Decreases the expression of TNF- $\alpha$ and ICAM-1 mRNA                        | (58)      |
| 11     | Curcumin  | Alleviated CIA mediated inflammation, synovial hyperplasia                       | (59)      |
| 12     | Aloin   | Suppresses receptor activator of nuclear factor kappa- $\beta$                   | (60)      |
| 13     | Cannabidiol   | Inhibition of inflammatory mediators   | (61)      |
| 14     | Puncalagin  | Reduction of TNF-alfa and pro inflammatory compounds                             | (62)      |
| 15     | Cinnamaldehyde  | Inhibition of PI3/AKT signaling pathway  | (63)      |

constituents.

There are numerous researches that support the use of herbal medicinal plants in RHA management. The phytochemicals have the potential to be useful against RHA. Flavonoids (luteolin), anthraquinone glycoside (Emodin), caffeic acid ester (Rosmarinic acid), stilbenoid polyphenol (Resveratrol), carotenoids (cryptoxanthin, phenolic xanthonoid (Mangiferin), and alkaloids (Piperlongumine) are among these phytochemicals (64). *Zingiber officinale*, *Trigonella foenum-graecum* and *Withania somnifera* were studied for the potential phytochemicals used for RHA management (64). The usual method of RHA management involves the modulation of pro-inflammatory pathways. The studies also revealed the involvement of reactive oxygen species in RHA, so the treatment and prevention include antioxidants. Plants and herbs are good source of natural antioxidants which provides free radical scavenging activity and anti-inflammatory activity by suppressing nitric oxide, IL-6, IL-1 $\beta$  and chemokines. The role of flavonoids in RHA treatment has also been discussed (65, 66). Pomegranate extract has been proven to be a potent for RHA treatment in a clinical trial showing the successful results by reduction in joint swelling, pain severity, rate, and level of erythrocyte sedimentation, etc. (67). Naturally present flavonoids in fruits and vegetables and herbs modulate the NF- $\kappa$ B signalling pathway and inhibit the transcription of the inflammatory factors present in the synovial joints.

The signalling pathways like IL-1 $\beta$ , PGE2, COX, MMP, p38, ERK1/2, JNK, and MAPKs expressions are inhibited through the anti-inflammatory and antioxidant properties of green tea, propolis, grapefruit, etc. (68). Synovial hyperplasia is inhibited by ERK MAPK along with angiogenesis and osteoclastogenesis downregulation which further helps in RHA suppression (69). The synthesis of nitric oxide is inhibited, and the levels of pro-inflammatory cytokines including IL-6, COX-2, TNF- $\alpha$ , iNOS, and IL-1 $\beta$  are reduced in plants enriched with alkaloids, which has been shown to considerably reduce the inflammatory response (64).

The difficulty with natural products is their poor absorption and increase in the amount can lead to toxicity and unwanted side effects. Nanoparticles are being used in clinical practices by encapsulating the bioactive natural particles to increase the *in vivo* stability, extend their circulation time and controlled and sustained release (70). The therapy of RA may one day involve targeting the enzymes and their derivatives, and these targeted herbal medical items would prove to be excellent RA treatments. Therefore, it is important to support the multidisciplinary research efforts that aim to describe the precise molecular mechanisms, screen and discover innovative herbal products, and examine the detailed biological activities of current herbal products. The discovery, testing, and development of safe and efficient herbal products for the treatment of RA and other inflammatory and autoimmune-mediated illnesses would be facilitated and accelerated by these measures (71).

## Future Prospects

Research is presently being performed in a variety of fields, including the creation of novel biologic medications, gene therapy, and regenerative medicine. The creation of revolutionary biologic medicines that specifically target molecules involved in the immune response that causes RA is a promising research area. Traditional RA therapy has limits, necessitating the development of innovative therapeutic techniques. Because of their structural variety and biological activity, plant-derived bioactive chemicals have enormous potential. High-Throughput Screening (HTS) approaches allow for the quick screening of vast plant chemical libraries, allowing the discovery of lead compounds with potential therapeutic actions against RA. These approaches, in conjunction with robotic automation and miniaturisation, enable effective screening of a wide range of plant extracts and chemicals. Computational techniques, such as virtual screening and computer-aided drug creation, enable the prediction of bioactive molecules from plant sources through the screening of enormous chemical databases. These approaches help identify prospective candidates with particular interactions with RA targets more quickly. Approaches based on omics, such as the integration of genomes, transcriptomics, proteomics, and metabolomics, provide complete insights into plant-derived substance production processes. Omics data can be used to prioritise plant species or specific tissues for screening, thereby increasing the finding of bioactive chemicals with RA relevance. Plant-derived compounds can influence immunological responses in RA by balancing pro-inflammatory and anti-inflammatory mediators. They have the ability to inhibit autoantibody synthesis, alter T-cell responses, and influence the function of immune cells involved in RA pathogenesis.

Reverse pharmacology is the identification and selection of traditional Ayurvedic and Siddha therapeutic formulations that have historically been used for rheumatic illnesses such as RA. For identifying viable treatments, ancient writings, manuscripts, and experienced practitioners are invaluable resources. The discovered formulations are subjected to extensive phytochemical investigation in order to determine the bioactive components that are responsible for their medicinal benefits. Following that, bioactivity screening employing *in vitro* and *in vivo* models helps validate the formulations' anti-inflammatory, immunomodulatory, and antioxidant capabilities. Methods of standardisation ensure that traditional medical compositions are consistent and of high quality. This entails developing marker substances, dosage formulations, and production techniques that adhere to current regulatory norms. To scientifically validate the efficacy, safety, and pharmacokinetic properties of the selected formulations, rigorous clinical trials are conducted. These trials look at how they affect disease activity, symptom alleviation, joint inflammation, immunological modulation, and quality of life in RA patients. Reverse pharmacology is a promising strategy for revalidating the activity of Ayurveda and Siddha for the treatment of Rheumatoid Arthritis. Traditional medicinal compositions'



efficacy can be scientifically validated by blending traditional wisdom with modern scientific procedures such as phytochemical analysis, bioactivity screening, and clinical trials. This approach not only helps to discover effective and safe treatments for RA, but it also promotes the preservation and appreciation of traditional medicine's rich past.

Herbal medicines provide an alternative to traditional drugs. Understanding the cost-effectiveness and ease of access to raw materials utilised in herbal RA treatments is critical for their practical application in healthcare. Herbal medicines frequently use plant-based components that are less expensive than manufactured pharmaceuticals. This characteristic contributes to the cost-effectiveness of herbal treatments for RA, making them more accessible to individuals of various financial means. The world's different ecosystems provide an abundance of medicinal plants, many of which are employed in RA herbal treatments. These plants are frequently abundant in local areas, making them widely accessible to communities worldwide. Many plants used in herbal medicines may be grown, making them sustainable and available all year. Home gardens, community gardens, and specialised farms can provide a continual supply of raw materials for herbal formulations, minimising reliance on imported or rare resources. Herbal therapies for Rheumatoid Arthritis use low-cost, readily available basic materials, making them accessible to a wide spectrum of people. Consideration of the economic and practical benefits of herbal remedies is vital for a holistic and patient-centred approach to RA care. With proper quality control and research, herbal treatments can provide cheap and sustainable solutions in the management of RA, encouraging holistic healthcare and patient empowerment. Future research should concentrate on finding the most potent natural remedies and creating standardised formulations that can be applied in clinical experiments. More study is also required to examine the possibility of combining conventional medications with natural remedies in a treatment regimen to help rheumatoid arthritis patients.

## Conclusion

Rheumatoid arthritis is affecting many peoples worldwide. It is a progressive disease that can lead to disability and reduced life expectancy if left untreated. Early diagnosis and treatment are crucial to prevent or minimize joint damage and improve the patient's quality of life. While there is no cure for RA, there are several treatment options available that can help manage the symptoms and slow the progression of the disease. Current treatments focus on reducing inflammation and pain, preserving joint function, and improving the overall quality of life. However, there is still a need for more effective and targeted therapies that can address the underlying mechanisms of RA. There are many pharmacological treatments for RA, including nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs, but herbal allies like ginger (*Zingiber officinale*), Chinese wolfsbane (*Aconitum carmichaelii*),

guggul (*Commiphora wightii*), cinnamon (*Cinnamomum cassia*), etc. are also quite popular. They cause the body to respond in pharmacological, anti-inflammatory, and immunological ways. When a disease is present, certain cell signalling pathways, such as NF- $\kappa$ B, ERK, p38 MAP kinase, and JNK, are targeted, leading to the proliferation of B and T cells and the production of cytokines using the herbal allies mentioned above. Natural products, including plant species, have been used traditionally for the treatment of RA, and there is growing evidence supporting their potential therapeutic benefits. However, more research is needed to fully understand their mechanisms of action and safety profiles. In conclusion, continued research and development of new and innovative therapies are necessary to improve the lives of those living with RA. Clinicians should continue to individualize treatment plans, considering the patient's overall health and disease severity, to provide the best possible care.

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## Authors' contributions

AS, MK, and SS contributed to the design and wrote the first draft of the manuscript. RKKO assisted with the acquisition, collecting, and compilation of literature for the current review. NS helped to prepare the figures and tables. IR came up with the idea and edited the article after it was reviewed. The final manuscript was read and approved by all the authors.

## Compliance with ethical standards

**Conflict of interest:** Authors do not have any conflict of interests to declare.

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