Exploring Treatment Options for Rheumatoid Arthritis: A Comprehensive Review of Herbal and Synthetic Therapies

Sidhant Sharma[1], Balwinder Singh[1], Kiran Bala[1], Anshul Thakur[1], Manisha[1], Shiv Kumar Kushwaha[1*], Mahendra Singh Ashawat[2]

1. Department of Pharmacology, Laureate Institute of Pharmacy, Kathog, H.P.-176031, India.

2. Department of Pharmaceutics, Laureate Institute of Pharmacy, Kathog, H.P.17031, India

Address of Correspondence:
Mr. Shiv Kumar Kushawaha,
Department of Pharmacology,
Laureate Institute of Pharmacy,
Kathog, H.P.176031, India
Email: shiv.kushawaha@gmail.com,
Orchid Id: 0000-0002-3692-2774

Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and progressive joint damage. The pathophysiology of RA involves a complex interplay between immune dysregulation, synovial inflammation, and tissue destruction. This review article provides an overview of the current understanding of RA pathophysiology and the status of the disease, including diagnostic criteria, disease progression, and associated complications. The increasing interest in alternative treatment options for rheumatoid arthritis (RA), including herbal therapies, has captured attention in recent years. This review article dedicates to delve into the utilization of herbal treatments in managing RA. Numerous herbs and botanical extracts have demonstrated encouraging effects in reducing inflammation and modulating the immune response, presenting a potential adjunctive strategy for RA treatment. The article delves into the mechanisms of action, efficacy, and safety profiles associated with commonly employed herbal treatments. Furthermore, the review article provides insights into the synthetic treatment approaches for RA, encompassing disease-modifying antirheumatic drugs (DMARDs) and biologic agents. The current therapeutic strategies, including conventional synthetic DMARDs, targeted synthetic DMARDs, and biologic DMARDs, are thoroughly examined, shedding light on their respective mechanisms of action and clinical efficacy. Overall, this review article provides a comprehensive overview of the pathophysiology of RA, the current understanding of the disease, and the use of both herbal and synthetic treatments. It highlights the potential benefits and limitations of herbal therapies and emphasizes the importance of personalized treatment approaches in managing RA. Further research and clinical trials are needed to better understand the efficacy, safety, and long-term outcomes of herbal and synthetic treatments in RA management.

Keywords: *Rheumatoid arthritis, Pathophysiology, Current status, Herbal treatment, Synthetic treatment, Alternative therapies, Herbal therapies, Anti-inflammatory, Immunomodulatory effects*

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune condition characterized by inflammation that affects various parts of the body. Initially, rheumatoid arthritis usually affects the smaller joints before advancing to larger ones, while also having an impact on the skin, eyes, heart, kidneys, and lungs. This condition often results in damage to the bones and cartilage within the joints, while also increasing the vulnerability of tendons and ligaments to injuries [1]. The disease can manifest at any age and has a higher occurrence in women, with a ratio of two to three times more cases compared to men [2]. The peak incidence of this prevalent form of inflammatory arthritis is commonly observed during the sixth decade of life. Estimates indicate that approximately 25 out of every 100,000 men and 54 out of every 100,000 women are affected by this condition, leading to an estimated 250,000 hospitalizations and around 9 million doctor visits annually in the United States [3-5]. Unlike other forms of arthritis, rheumatoid arthritis synovitis has a notable tendency to breach tissue boundaries and invade the bone and cartilage within the joints, forming what is known as pannus. Insufficient management of the condition can have serious consequences, such as substantial impairment that may impact one's ability to earn a living, potentially leading to early retirement. In severe instances, it can even result in untimely death [6, 7].

The goals of treating rheumatoid arthritis (RA) are to minimize joint pain and inflammation, improve joint function, and prevent joint damage and deformity. Typically, treatment approaches encompass a blend of medications, weight-bearing exercises, patient education, and periods of rest. The therapeutic approaches are tailored to cater to the specific needs of every patient, taking into account various factors such as the progression of the disease, the affected joints, age, overall health, occupation, adherence to treatment, and level of understanding about the condition. This individualized approach guarantees that the treatment is specifically tailored to meet the unique circumstances and needs of every patient [8, 9].

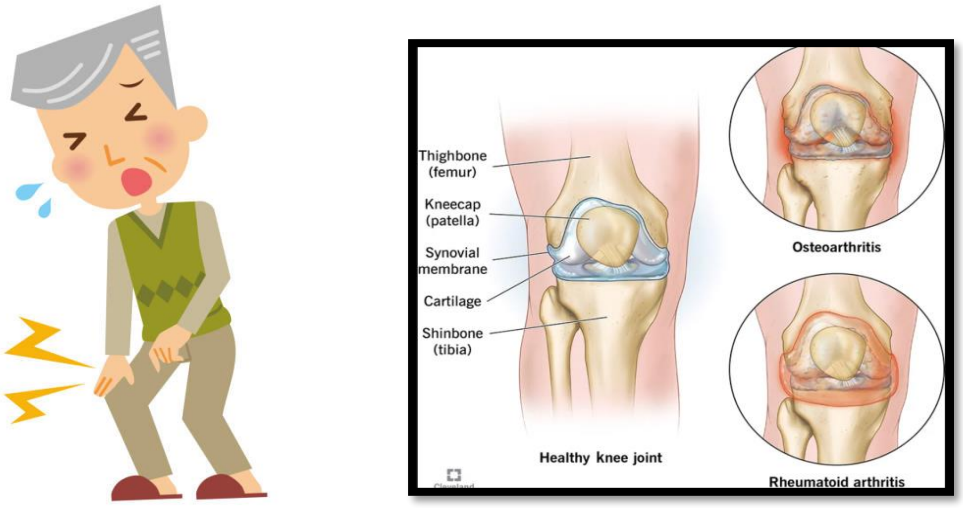


Fig.1.Joint Pain

2. Pathophysiology:

Recent research indicates that the development of autoimmune inflammatory arthritis is not solely explained by the conventional expansion of antigen-driven effector T-cell clones that target synovial joints. In contrast to early findings in rodent arthritis models, it is now evident that the differentiation pathways of T-cells in autoimmune inflammatory arthritis do not strictly adhere to the conventional polarized pathways. However, in individuals with established rheumatoid arthritis (RA), it has been observed that T helper (Th)1 cells expressing interferon (IFN)-γ and tumor necrosis factor (TNF)-α are present in the synovial joints [10, 11]. This deviation from the expected T-cell differentiation pathways may be influenced not only by the inflamed and hypoxic environment in the synovium, which is known to impair T-cell receptor (TCR) responsiveness, but also by the accelerated immune senescence that may occur during the early phase of the disease [12, 13]. The anatomical site of T-cell differentiation in early rheumatoid arthritis may impact the pathway. A recent analysis of synovial fluid in patients with early inflammatory synovitis showed unexpected Th2 profiles (IL-4, IL-5, IL-13), while subsequent RA patients lacked these cytokines. Synovial T cells in established rheumatoid arthritis display reduced levels of IFN-γ, IL-10, and TNF-α, while IL-2 and IL-4 expression is minimal. Notably, an intriguing discovery is the link between the severity of RA and an IL-4R allelic variant that hinders IL-4R signaling and Th2 differentiation [14, 15]

CD4 T cells have a pivotal role in initiating and sustaining the immune response in arthritis. Once activated, CD4 T cells undergo differentiation into distinct subsets, including Th1, Th2, Th17, and Treg cells, each serving specific functions. Th1 cells generate pro-inflammatory cytokines like interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which contribute to tissue damage and inflammation observed in arthritis. Conversely, Th2 cells produce cytokines such as interleukin-4 (IL-4) and IL-13, which play a role in allergic and autoimmune responses [16].

Macrophages, essential components of the innate immune system, have a significant role in arthritis. When activated, macrophages secrete pro-inflammatory cytokines like TNF-α, IL-1, and IL-6, which stimulate inflammation, attract immune cells, and cause tissue destruction. Additionally, macrophages engulf cellular debris through phagocytosis and produce matrix metalloproteinases (MMPs), which contribute to the damage of joints [17].

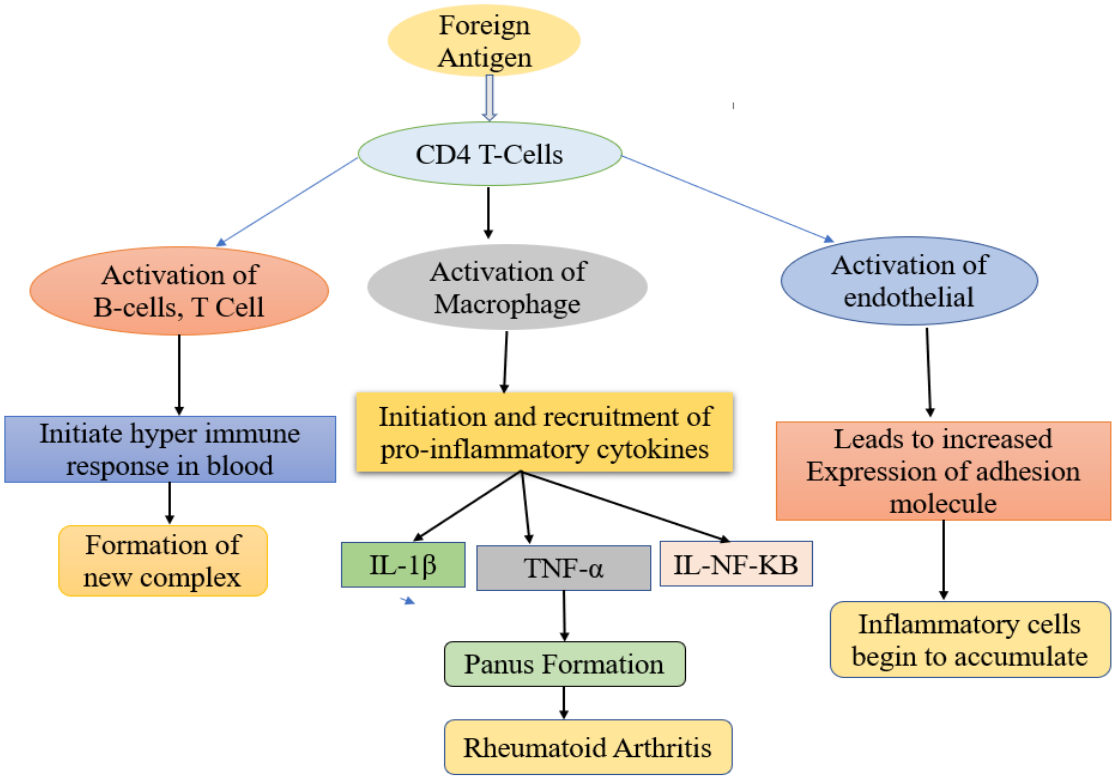


Fig.2.Pathophysiology Of Arthritis

3. Herbal Drug Treatment

Numerous herbs have shown effectiveness in managing inflammation among individuals with rheumatoid arthritis (RA). These herbs generally impact multiple immunological pathways instead of targeting a single specific inflammatory pathway. The concept of modulating inflammation, rather than simply having anti-inflammatory properties, has been extensively explored in the context of herbal therapy [18].

3.1 Black Pepper

Biological Name: Piper nigrum Linn.

Common Name: Pepper

Family: Piperaceae

Fig.3.Black Pepper

Properties:
It enhances the secretion of gastric juice and improves the bioavailability of certain medications. Piperine, extracted from black pepper, was administered orally at doses of 20 and 100 mg/kg/day for eight days to treat acute paw arthritis induced by carrageenan [19, 20].

3.2 Banyan Tree

The anti-rheumatic activity of the methanolic extract derived from the bark of Ficus bengalensis (MFB) was investigated using various arthritis models induced by agar, formalin, and Freund's complete adjuvant. The extract exhibited a dose-dependent inhibition of both phases of formalin-induced pain and demonstrated a significant inhibitory effect on edema, particularly in secondary immunological arthritis. The methanolic extract of Ficus bengalensis bark contained a variety of phytochemicals, including terpenoids, alkaloids, glycosides, flavonoids, and steroids. The presence of flavonoids, tannins, saponin, and steroids in the extract indicates its potential anti-rheumatic properties and the possibility of affecting the immune system [21-23]

Biological Name: Ficus bengalensis Linn.
Common name: Banyan tree or Barga
Family: Moraceae

Fig.4. Banyan Tree

3.3 Curcuma:

Turmeric, a spice derived from the roots of the Curcuma plant, is commonly used in cooking. Curcumin, a polyphenol extract found in turmeric, has been utilized in traditional Chinese and Ayurvedic medicine for its antioxidant and anti-inflammatory properties. Curcuma exhibits anti-inflammatory effects through multiple mechanisms. Research has shown that Curcuma treatment successfully inhibits the activation of signaling pathways such as NF-B, protein kinase B (Akt), and MAPK, resulting in a notable reduction in the production of inflammatory mediators. These mediators include interleukin (IL)-1, tumor necrosis factor-alpha (TNF-), IL-8, nitric oxide (NO), and various matrix metalloproteinases (MMPs) [24, 25].

Botanical name: Curcuma longa Linn.
Other Name: Turmeric root, Indian saffron Plant
Family: Zingiberaceae

Fig.5.Curcuma

3.4 Aloe

Aloe barbadensis is grown in several regions of India, including the north-west Himalayan region, as well as in Europe. Aloe is an effective anti-inflammatory and immune system stimulant. Aloe extract used topically reduces inflammation and arthritis in Sprague Dawley rats with adjuvant-induced arthritis. It is also used as a blood purifier, anti-inflammatory, diuretic, uterine tonic, spermatogenic, laxative, purgative, and fever reducer. It also possesses antibacterial and antifungal qualities [26, 27]

Botanical Name: Aloe barbadensis

Other Name: Curacao aloe, Lily of the desert

Family: Liliaceae

Fig.6.Aloevera

3.5 Ashwagandha

Ashwagandha, commonly referred to as Indian ginseng, is a significant old plant. Alkaloids and steroidal lactones are thought to be responsible for the root's pharmacological effect. Withanine, pseudowithanine, tropine, pseudo-tropine, somniferine, and somnine are the most prevalent alkaloids. In adjuvant-induced arthritic rats, oral treatment of Withenia somnifera Linn.root powder had an anti-arthritic effect [28].

Botanical Name: Withania somnifera Linn.

Other Name: Winter cherry,withania root

Family: Solanaceae

Fig.7.Ashwagandha

3.6 Green Tea

Green tea is derived from the plant Camellia Sinensis, belonging to the Theaceae family. Its active constituents include catechins and flavanols, which contribute to its beneficial properties. Among these, epigallocatechin is a particularly important catechin. In a study involving mice with collagen-induced arthritis, administration of green tea led to a reduction in inflammatory mediators such as COX, IFN, and TNF. Furthermore, the arthritic joints of the mice showed decreased levels of total immunoglobulin and type II collagen-specific IgG [29, 30].

Biological Name: Camellia sinensis Linn.
Common Name: Green tea extract, Chinese tea
Family: Theaceae

Fig.8.Green Tea

3.7 Mangifera Indica

The mango species Mangifera indica is a member of the Anacardiaceae family. Mangiferin,isomangiferin, gallic acid, polyphenols, and other ingredients are present. Mangifera indica's methanolic extract shown anti-inflammatory properties and was reported to significantly reduce arthritic index, paw edoema, and rheumatoid factor [31-33].

Botanical Name: Mangifera indica Linn

Other Name: mamidi, manga

Family: Anacardiaceae

Fig.9.Mango

4. Synthetic Treatment of Arthritis

The treatment approach known as the "pyramid method" initially involves prescribing bed rest and non-steroidal anti-inflammatory drugs (NSAIDs). As the disease progresses, more effective disease-modifying antirheumatic drugs (DMARDs) are added to the treatment regimen [34].

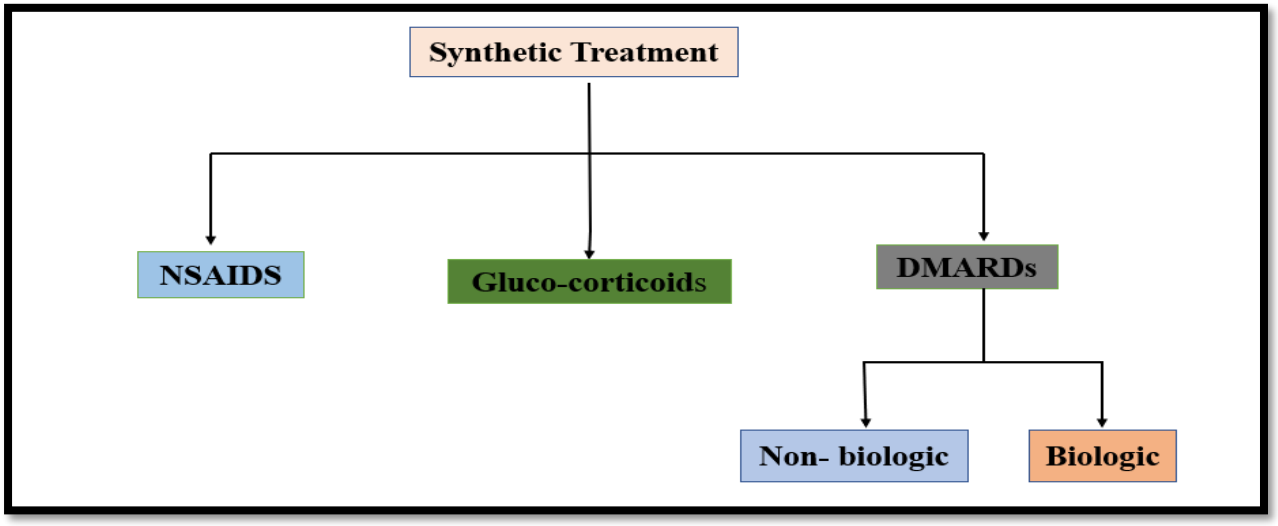


Fig.10.Classification of Synthetic Treatment

4.1 NSAIDs

NSAIDs are typically used as the first line of treatment for RA, osteoarthritis, and other musculoskeletal conditions. They are typically used to treat the disease's symptoms; they have no impact on the disease's underlying cause. These medications lessen swelling and pain.

Mechanism of Action:

Non-steroidal anti-inflammatory drugs (NSAIDs) exert their effects by selectively inhibiting the enzyme cyclooxygenase (COX), which is involved in the production of inflammatory mediators called prostaglandins. Prostaglandins play a crucial role in promoting inflammation, pain, and fever. COX exists in two isoforms: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constitutively expressed in many tissues and is involved in physiological functions such as maintaining normal renal function and protecting the gastric lining. COX-2, on the other hand, is induced during inflammation and plays a major role in generating prostaglandins that contribute to pain and inflammation. By selectively inhibiting COX-2, NSAIDs help reduce inflammation and alleviate associated symptoms. However, it's important to note that some NSAIDs may also inhibit COX-1 to varying degrees, which can lead to potential side effects such as gastrointestinal irritation and impaired blood clotting [35, 36][28-29]

Classification of NSAIDs:

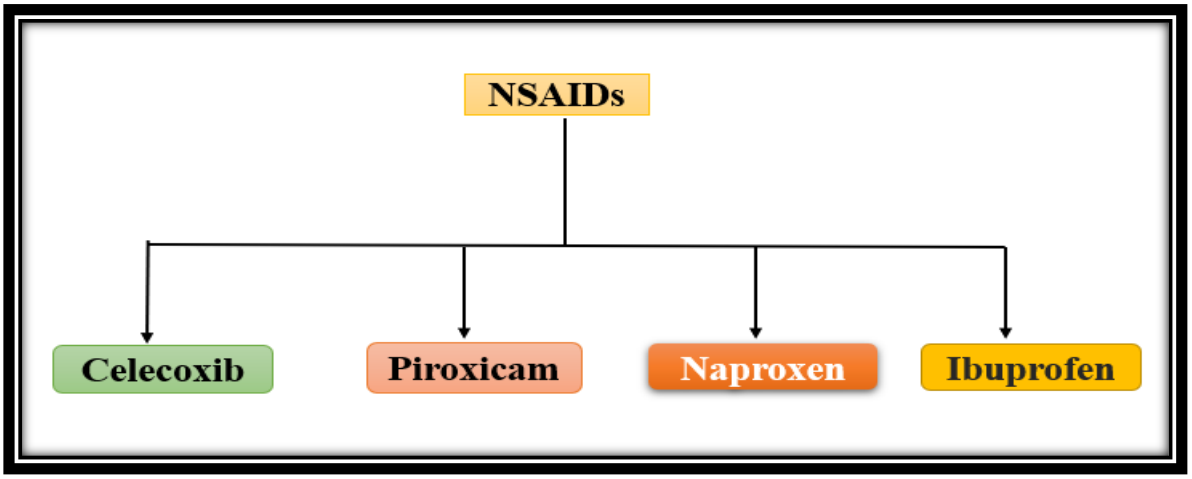
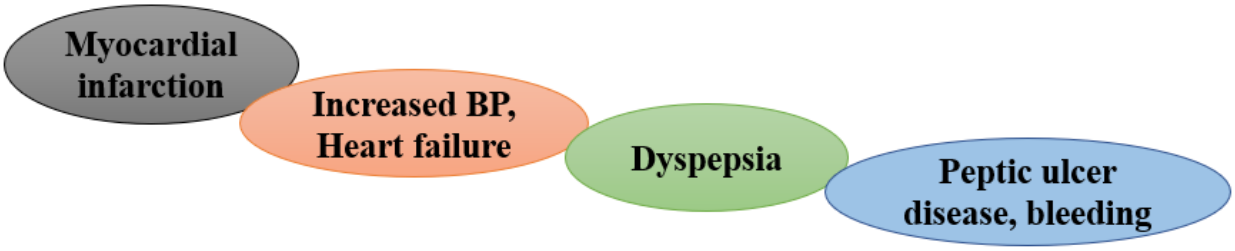


Fig.11.NSAIDs

Side Effects:



4.2 Glucocorticoids:

The second most frequently prescribed medication for the treatment of RA is corticosteroids. These substances have potent analgesic and anti-inflammatory effects. Corticosteroids should only be used after trying every other form of treatment for RA, according to the National Institute for Health and Clinical Excellence (NICE), because they can cause serious side effects like Cushing's syndrome, weight gain, cataracts, hypertension, and severe osteoporosis and fractures [37, 38].

Mechanism of Action:

Decreased capillary permeability and suppression of macrophage accumulation.

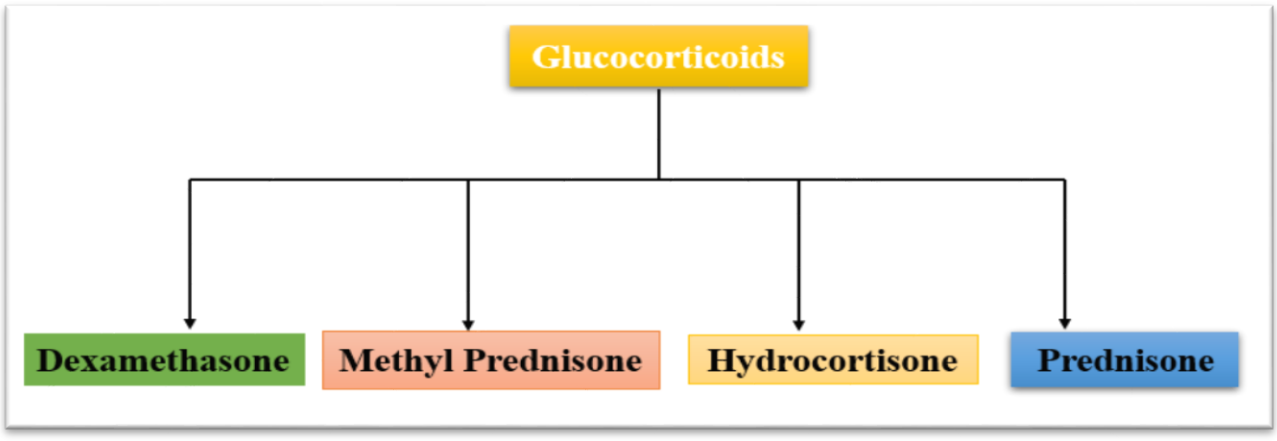


Fig.12.Classification of Glucocorticoids

Side Effects:

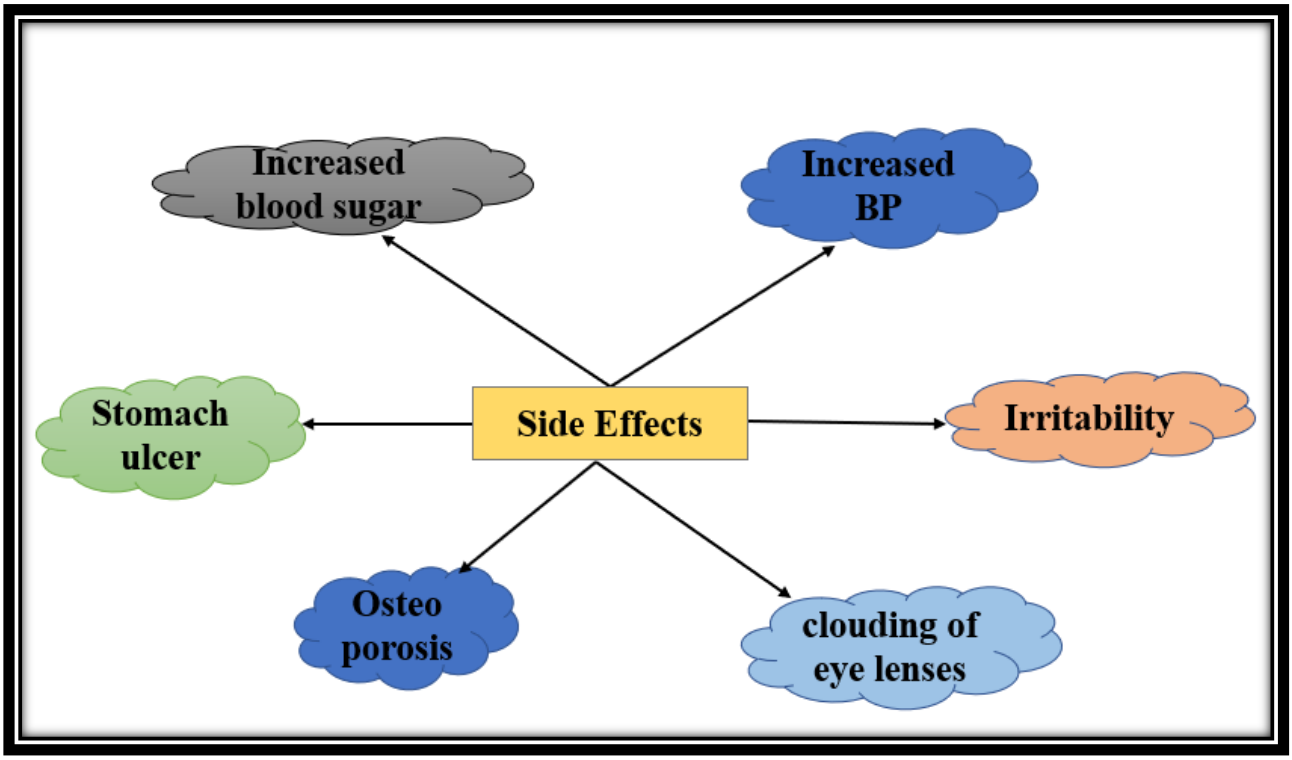


Fig.13.Side Effects

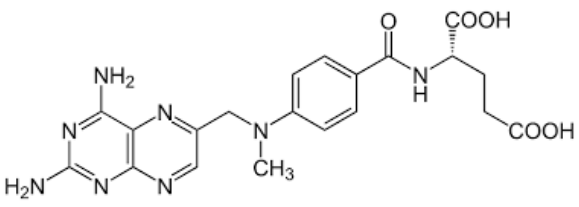
4.3 Nonbiologic DMARDs

Methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ), and sulfasalazine (SSZ), which are more frequently used than other medicines with a lesser efficacy and safety profile, such as gold salts, azathioprine, d-penicillamine, cyclosporine, minocycline, and cyclophosphamide.

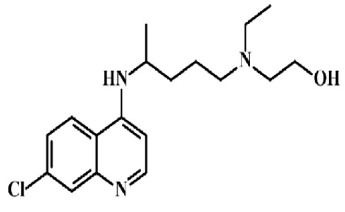
Mechanism of Action:

The hyperactive immune system is non-targetedly suppressed by their modes of action, reduces the generation of autoantibodies by B cells and T cells, and reduces the release of inflammatory cytokines [39, 40]

Structure:



Methotrexate



Hydroxychlorquine

Side Effects:

Hairfall

Mouth Ulcer

Nausea

Abdominal Pain

4.4 Biologic DMARDs

If first-line therapy is not tolerated or is unsuccessful, DMARDs or tsDMARDs are advised. tsDMARDs, especially the family of Janus kinase inhibitors (JAKi), offer the advantage of being orally taken [41].

Mechanism of Action:

Inhibits Interleukin – 6 receptor.

Classification:

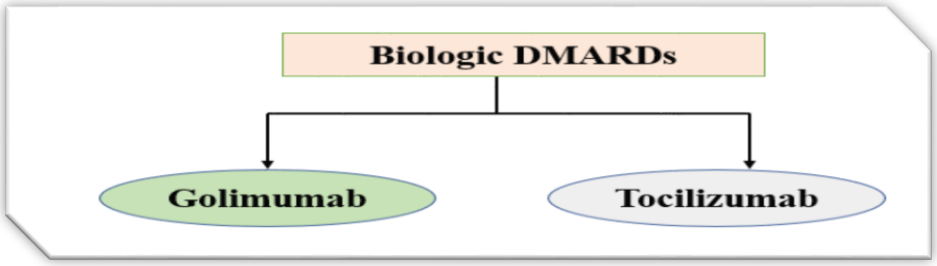
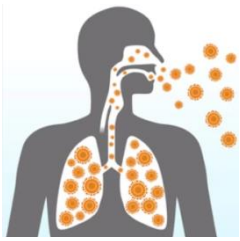


Fig.15.Classification of bDMARDs

Side Effects:

Headache

Hypertension



Respiratory Tract Infection

Conclusion:

It is a well-known truth that the traditional medical system has always played a significant part in providing for the needs of the entire world's population. One of the most prevalent auto-immune inflammatory diseases and the leading cause of disability in both developed and developing nations is arthritis. The medicinal properties of herbs offer active ingredients with no or minimal side effects, which may be helpful in controlling arthritis.

Acknowledgment:

The author is thankful to Dr. Ran Singh, Managing Director, Laureate Institute of Pharmacy for providing resources and facilities for this research work.

Data availability: Not applicable.
Conflict of interest: Authors declare that they have no conflict of interest.
Ethics approval: Not applicable.
Consent to participate: Not applicable.
Consent for publication: Not applicable. Code availability: Not applicable.

Reference

1. *Smolen, J.S., et al., Rheumatoid arthritis. Nature Reviews Disease Primers, 2018.* ***4****(1): p. 18001.*
2. *Myasoedova, E., et al., Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955–2007. Arthritis & Rheumatism, 2010.* ***62****(6): p. 1576-1582.*
3. *Harris, E., Clinical features of rheumatoid arthritis. Kelley's textbook of rheumatology, 2000.*
4. *Abdulkader, O.A.F., K. Qushmaq, and F. Aljishi, Tocilizumab efficacy and safety in rheumatoid arthritis patients after inadequate response to disease-modifying anti-rheumatic drugs or anti-tumor necrosis factor. Annals of Saudi Medicine, 2016.* ***36****(3): p. 190-196.*
5. *Kwoh, C., et al., American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis & Rheumatology, 2002.* ***46****(2): p. 328-346.*
6. *Choi, H.K., et al., Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. The Lancet, 2002.* ***359****(9313): p. 1173-1177.*
7. *Guo, Q., et al., Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res, 2018.* ***6****: p. 15.*
8. *Kavuncu, V. and D. Evcik, Physiotherapy in rheumatoid arthritis. MedGenMed, 2004.* ***6****(2): p. 3.*
9. *Cooney, J.K., et al., Benefits of exercise in rheumatoid arthritis. J Aging Res, 2011.* ***2011****: p. 681640.*
10. *Kanik, K., et al., Distinct patterns of cytokine secretion characterize new onset synovitis versus chronic rheumatoid arthritis. The Journal of rheumatology, 1998.* ***25****(1): p. 16-22.*
11. *Rönnelid, J., et al., Production of T-cell cytokines at the single-cell level in patients with inflammatory arthritides: enhanced activity in synovial fluid compared to blood. British journal of rheumatology, 1998.* ***37****(1): p. 7-14.*
12. *Cope, A.P., Studies of T-cell activation in chronic inflammation. Arthritis Research & Therapy, 2002.* ***4****(3): p. 1-15.*
13. *Vallejo, A.N., C.M. Weyand, and J.J. Goronzy, T-cell senescence: a culprit of immune abnormalities in chronic inflammation and persistent infection. Trends in molecular medicine, 2004.* ***10****(3): p. 119-124.*
14. *Raza, K., et al., Early rheumatoid arthritis is characterized by a distinct and transient synovial fluid cytokine profile of T cell and stromal cell origin. Arthritis research & therapy, 2005.* ***7****: p. 1-12.*

15. *Yudoh, K., et al., Reduced expression of the regulatory CD4+ T cell subset is related to Th1/Th2 balance and disease severity in rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 2000.* ***43****(3): p. 617-627.*
16. *Luckheeram, R.V., et al., CD4+T cells: differentiation and functions. Clin Dev Immunol, 2012.* ***2012****: p. 925135.*
17. *Kinne, R.W., et al., Macrophages in rheumatoid arthritis. Arthritis Research & Therapy, 2000.* ***2****(3): p. 189.*
18. *Yarnell, E. and K. Abascal, Herbs for curbing inflammation. Alternative & Complementary Therapies, 2006.* ***12****(1): p. 22-28.*
19. *Agrawal, S. and M. Paridhavi, Herbal drug technology. 2007: Universities press.*
20. *Bang, J.S., et al., Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1β-stimulated fibroblast-like synoviocytes and in rat arthritis models. Arthritis research & therapy, 2009.* ***11****(2): p. 1-9.*
21. *Manocha, N., et al., Anti-rheumatic and antioxidant activity of extract of stem bark of Ficus bengalensis. Res J Chem Sci, 2011.* ***1****(2): p. 2-8.*
22. *Kaur, A., P. Nain, and J. Nain, Herbal plants used in treatment of rheumatoid arthritis: a review. Int J Pharm Pharm Sci, 2012.* ***4****(4): p. 44-57.*
23. *Joseph, B. and S.J. Raj, An overview-ficus bengalensis Linn. Int J Pharm Sci Rev Res, 2011.* ***6****(1): p. 21-24.*
24. *Chin, K.-Y., The spice for joint inflammation: anti-inflammatory role of curcumin in treating osteoarthritis. Drug design, development and therapy, 2016: p. 3029-3042.*
25. *Aggarwal, B.B., Y.-J. Surh, and S. Shishodia, The molecular targets and therapeutic uses of curcumin in health and disease. Vol. 595. 2007: Springer Science & Business Media.*
26. *Joshph, B. and S. Raj, Pharmacognostic and pharmacology properties of Aloe vera. International journal of Pharmaceutical Sciences Review and Research, 2010.* ***4****(2): p. 106-109.*
27. *Davis, R.H., P.S. Agnew, and E. Shapiro, Antiarthritic activity of anthraquinones found in aloe vera for podiatric medicine. J Am Podiatr Med Assoc, 1986.* ***76****(2): p. 1-8.*
28. *Mirjalili, M.H., et al., Steroidal lactones from Withania somnifera, an ancient plant for novel medicine. Molecules, 2009.* ***14****(7): p. 2373-2393.*
29. *Ahmed, S., Green tea polyphenol epigallocatechin 3-gallate in arthritis: progress and promise. Arthritis research & therapy, 2010.* ***12****: p. 1-9.*
30. *Chopade, V., et al., Green tea (Camellia sinensis): Chemistry, traditional, medicinal uses and its pharmacological activities-a review. Pharmacognosy Reviews, 2008.* ***2****(3): p. 157.*
31. *Garrido-Suárez, B.B., et al., A Mangifera indica L. extract could be used to treat neuropathic pain and implication of mangiferin. Molecules, 2010.* ***15****(12): p. 9035-9045.*
32. *Garrido, G., et al., In vivo and in vitro anti-inflammatory activity of Mangifera indica L. extract (VIMANG®). Pharmacological Research, 2004.* ***50****(2): p. 143-149.*
33. *Garrido, G., et al., Analgesic and anti-inflammatory effects of Mangifera indica L. extract (Vimang). Phytotherapy Research: An international journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, 2001.* ***15****(1): p. 18-21.*
34. *Schumacher, H.R., J.H. Klippel, and W.J. Koopman, Primer on the rheumatic diseases, in Primer on the rheumatic diseases. 1993. p. 349-349.*

35. *Schnitzer, T.J., et al., The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis. Clinical therapeutics, 1999.* ***21****(10): p. 1688-1702.*
36. *Krug, H., et al., Tolerability and efficacy of nabumetone and naproxen in the treatment of rheumatoid arthritis. Clinical therapeutics, 2000.* ***22****(1): p. 40-52.*
37. *Hoes, J.N., et al., Current view of glucocorticoid co-therapy with DMARDs in rheumatoid arthritis. Nature Reviews Rheumatology, 2010.* ***6****(12): p. 693-702.*
38. *Buttgereit, F., et al., Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. Annals of the rheumatic diseases, 2010.* ***69****(7): p. 1275-1280.*
39. *Guo, Q., et al., Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone research, 2018.* ***6****(1): p. 15.*
40. *Bullock, J., et al., Rheumatoid arthritis: a brief overview of the treatment. Medical Principles and Practice, 2019.* ***27****(6): p. 501-507.*
41. *Bywall, K.S., et al., Patient preferences on rheumatoid arthritis second-line treatment: a discrete choice experiment of Swedish patients. Arthritis Research & Therapy, 2020.* ***22****(1): p. 1-10.*