A pharmacological review on role of various herbal and synthetic remedies for rheumatoid arthritis

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***Abstract*- Rheumatoid arthritis is the most prevalent type of systemic inflammatory arthritis. Women smokers, and anyone with a family history of the illness are the most commonly affected. The existence of at least one joint with obvious swelling that is unrelated to another illness is one of the prerequisites for diagnosis. Rheumatoid arthritis is more likely to be identified when more small joints are affected. Rheumatoid arthritis can be diagnosed in a patient with inflammatory arthritis if they have rheumatoid factor, anti- citrullinated protein antibodies, high C-reactive protein levels, or higher erythrocyte sedimentation rates. Patients who use medications should get tested for hepatitis B, hepatitis C, and TB. The use of anti-rheumatic drugs that can treat the condition is made possible by the early discovery of rheumatoid arthritis. The goals of the treatment include reducing joint discomfort and swollenness, preventing radiographic deterioration and visible deformity, and continuing daily activities including work and hobbies. Consider joint replacement in patients with severe joint damage whose symptoms are not adequately managed by conventional treatment.**

***Keywords* - Inflammation, herbal remedies, and rheumatoid arthritis.**

Introduction:-

Rheumatoid arthritis is one of the most prevalent chronic inflammatory conditions. The fact that it can also result in extra- articular symptoms like rheumatoid nodules, lung involvement or vasculitis, as well as systemic comorbidities, makes it important to consider it a syndrome even though it primarily affects the joints.[1] The therapeutic management of rheumatoid arthritis has undergone a therapeutic revolution in the last ten years, changing articular and systemic outcomes with the introduction of novel therapies, early therapy, new categorization criteria, and the use of more effective treatment methodologies. The majority of rheumatoid arthritis-related fields are covered in this article, including etiology, novel therapeutics, diagnosis, and therapeutic strategies. Full or strict remission is uncommon and typically not sustained without ongoing treatment, so rheumatoid arthritis still has a significant unmet need that should now be the focus of research efforts.[2]

Epidemiology:-

Chronic disease rheumatoid arthritis has a detrimental effect on society as well as the patient. The individual burden of musculoskeletal disorders is accompanied by a decline in quality of life, impairment of physical function, and accumulating comorbid risk. Along with substantial direct medical costs, functional disability, restricted employment options, and lower societal participation all add to the socioeconomic burden. It is crucial to identify inflammation early, treat it quickly, and develop novel therapy options to lessen or prevent further damage. Rheumatoid arthritis incidence in the northern hemisphere ranges from 0-5% to 1%, with a clear decline from urban to rural areas.[3] You have a three to five times greater chance of getting rheumatoid arthritis if someone in your family does. Additionally, twin concordance rates have increased, indicating that genetic factors may contribute to the onset of the disease. Recent estimates place the heritability of seropositive rheumatoid arthritis at 40–65%, while that of seronegative rheumatoid arthritis is only 20%.We now have a better understanding of the genetics of the disease, thanks to modern genomic tools and large, well-characterized clinical cohorts.[4] Genome-wide association studies using single nucleotide polymorphisms have discovered more than a hundred loci linked to the risk of developing rheumatoid arthritis; the majority of these loci relate to immunological processes. The HLA system, in particular HLA-DRB1, is strongly linked to the pathogenesis of peptide (and self-peptide) binding. Disease-associated alleles share common amino acid sequences in the peptide-binding groove, or so-called shared epitope. Further evidence that peptide binding plays a significant role in these conditions comes from the specific correlation of some HLA genotypes with more severe erosive illness and higher mortality. [5]

Pathophysiology:-

The etiology of RA is complex, like that of many other autoimmune diseases. Studies on monozygotic twins and familial clustering have revealed genetic susceptibility, with genetic risk constituting 50% of the risk of RA. Genetically, RA is linked to the human leukocyte antigens DR45 and DRB1, as well as a number of alleles collectively known as the common epitope. According to genome-wide association studies, the STAT4 gene and CD40 region are two additional genetic signatures that increase the risk of developing RA and other autoimmune diseases. In people who are genetically predisposed to the disease, smoking is the main environmental factor contributing to RA.[6] No particular pathogen has been shown to cause a reaction. Characteristics of RA include inflammatory processes that encourage the growth of synovial cells in joints. Later pannus development may lead to underlying cartilage damage and skeletal erosions. Interleukin-6 and tumor necrosis factor (TNF), two pro-inflammatory cytokines that are produced in excess, fuel the destructive process. [7]

Pharmacological Therapy:-
A preliminary evaluation of the treatment has been done. Recent guidelines have addressed the management of RA. For women of childbearing age, there are additional considerations because many drugs have negative effects on pregnancy. [8]Therapy for RA should begin once a diagnosis has been made in order to maintain quality of life (both personally and professionally), manage extra-articular manifestation, and prevent deformity (such as ulnar deviation) and radiographic damage (like erosions). The best method of treating RA is with DMARDs, or disease-modifying anti-rheumatic drugs. Rheumatoid arthritis can be treated with both herbal and synthetic medications. Physical and exercise therapy play a significant role in the treatment of RA in addition to pharmaceutical therapy. [9]

Herbal Drug use in the treatment of RA:-
Rheumatoid arthritis (RA), an inflammatory condition, orchestrates severe joint inflammation to destroy bone. Its production is mediated by a large number of innate and adaptive immune system cells, including neutrophils, mast cells, monocytes, dendritic cells, B cells, and T cells. For the treatment and maintenance of RA, numerous conventional drugs are frequently prescribed, but they have a number of negative side effects. CAM is a complementary therapy method for treating RA due to the disproportionate amount of bioactive components found in plant botanicals. The findings of the studies included in this review demonstrated that a number of signaling proteins and pro-inflammatory cells involved in the pathogenesis of RA were altered by these bioactive substances.[10]

Mechanism of various plants in Rheumatoids Arthritis:-
1.zingiber Officinale (Ginger):-
Due to gigerol's presence, ginger has its own anti-inflammatory properties. Ginger extract enhances circulation and prevents the release of lipoxygenase and cyclooxygenase. It is also used as a strong analgesic to relieve pain. [11]

2.Allium Cepa (onion):-
The high mineral and fiber content of onions is beneficial for maintaining joint health. Natural quercetin, which is important in inflammation, is present in onion extract. Onion is regarded as an anti-inflammatory drug because it contains quercetin. It also reduces inflammation in cases of arthritis. [12]

3.Cimbopogan Citratus (Lemon Grass):-
A herb with many medicinal properties is lemon grass.The bioactive compound in lemongrass, like geranial, has an anti-inflammatory effect on arthritis.It blocks the pathways of inflammation and inhibits the pro-anti-inflammatory molecule.Additionally, it eases pain. [13]

4.Curcuma longa (Turmeric):-
The plant known as turmeric is widespread throughout the world. It is an effective treatment for many diseases and disorders. Curcumin, Bis De Methoxy Curcumin (BDMC), and De Methoxy Curcumin (DMC) are all components of Curcuma longa, or turmeric.The presence of curcumin inhibits the release of pro-inflammatory mediators, thereby reducing inflammation. It also has a significant impact on pain management, making it a strong analgesic. [14]

5. Syzygium aromaticum (clove):-
A clove tree's flower bud is a clove. It has several medicinal uses in traditional usage. The bioactive component eugenol in cloves inhibits the activity of enzymes like cyclooxygenase and prostaglandins, which lowers inflammation in rheumatoid arthritis. Additionally, it eliminates free radicals, which contribute to inflammation and oxidative stress. [15]

6. Senna Occidentalis (coffee senna):-
One of the few medical uses for coffee senna or coffee weed is arthritis. Apegenin, which is present in the food, aids in blocking the inflammatory pathways. [16]

7. Ocimum basilicum (Scent leaf):-
Another name for scent leaf is basil. It has a number of medicinal properties. As an autoimmune disorder, arthritis exhibits immunomodulation and inhibits the release of a number of inflammatory mediators. This plant demonstrates a powerful role in the treatment of rheumatoid arthritis through this mechanism.[17]

8. Nauclea latifolia (Pin cushion):-
It comes from Africa. Rare plant with a very limited number of medicinal uses. The research journal reports that it has a strong anti-inflammatory effect and significantly improves arthritis. [17]

9. Cyperus articulates (Tiger nuts):-
Tiger nut is another name for it.Due to the bioactive compounds it contains, it may have an anti-inflammatory effect. Because there is a lack of scientific evidence regarding this plant, it is unclear how it works to reduce inflammation. [18]

10. Tamarindus indica (Tamarind):-
The fruit tamarind is renowned for having a sweet and sour flavor.Polyphenol is the primary bioactive substance found in tamarid fruit. Due to their antioxidant properties and capacity to reduce both oxidative stress and inflammation, polyphenolic compounds have the ability to reduce inflammation. [18]

11. Piper guineese (Ashanti peeper):-
It comes from West Africa. widely used for medicinal purposes in the West African region. The proper mechanism of anti-inflammation has not been established due to a lack of scientific research. [19]

12. ***Securidaca longepedunculata (Rhodesian violet):-***
It comes from Africa. It is used in Africa to treat a variety of medical conditions, arthritis being one of them. Because flavonoids are present, it has demonstrated anti-inflammatory properties.Flavonoids have potent antioxidant properties in addition to inhibiting a number of inflammatory enzymes, including prostaglandin and leukotriene. [20]

13. ***Leptadenia hastate (Saltbush):-***
The plant may have a small number of health benefits. These are mostly present in environments that are salty. Lupeol, a bioactive compound, has demonstrated an anti-inflammatory effect in rheumatoid arthritis as a result of its presence. [21]

14. Piper nigrum (Black Peeper):-
Every household regularly uses black pepper. It has a number of therapeutic applications in the traditional medical system. "Kala Mirch" is another name for black peeper. This reduces inflammation by stifling the different mediators involved in inflammation. [22]

15. Cola nitida (Kola Nut):-
Some parts of Africa use kolanut trees for their nuts. In the case of rheumatoid arthritis, it has strong anti-inflammatory properties. [23]

16. Allium sativum (Garlic):-
One well-known common household item is garlic. It also functions well for household chores and has a number of therapeutic benefits. It regulates the inflammatory mediators in Rheumatoid arthritis that cause the inflammation in the affected joints. [24]

17. Vernonia amygdalina (Bitter leaf):-
In some areas, this plant is frequently used to treat rheumatoid arthritis.Antioxidant properties help to reduce inflammation and oxidative stress. [25]

18. Ocimum gratissimum (Clove Basil):-
A very common plant used in traditional medicine is clove basil. It has a variety of therapeutic qualities. By preventing the release of cytokines and inflammatory enzymes, arthritis inflammation can be reduced. [26]

19. Capsicum annuum (Small Chilli Pepper):-Capsaicin, a bioactive compound found in small chillies, prevents the release of neuropeptide.which is crucial to inflammation.Small chilli pepper exhibits anti-inflammatory properties in this manner. [27]

20. Solanum melongena (Eggplant):-
Very little anti-inflammatory activity exists in eggplant. It suppresses inflammatory mediators, demonstrating anti-inflammatory activity in rheumatoid arthritis as a result. [28]

SL NO.	PLANT NAME	FAMILY	PARTS USED	COMMON NAME	BIOACTIVE COMPOUND
1	*Zingiber Officinale*	***Zingiberaceae***	Rhizome	Ginger	Gingerol,Shogaol[11]
2	*Allium cepa*	***Zingiberaceae***	Scale	Onion	Quercetin[12]
3	*Cymbopogon citratus*	***poeceae***	Leaves	Lemon grass	Geranial ,neral[13]
4	*Curcuma longa*	***Zingiberaceae***	Rhizome	Turmeric	Curcumin[14]
5	*Syzygium aromaticum*	***Myrtaceae***	Whole	clove	Eugenie[15]
6	*Senna occidentalis*	***Leguminoseae***	Leaves	Coffee senna	Apigenin[16]
7	*Ocimum basilicum*	***Lamiaceae***	Leaves	Scent leaf	(VitaminP) Rutin[17]
8	*Nauclea latifolia*	***Rubiaceae***	Stem, roots, leaves	Pin cushion	Caffeic acid[17]
9	*Cyperus articulatus*	***Cyperaceae***	Rhizomes	Tiger nut	β-Caryophyllene oxide,α-pinene[17]
10	*Tamarindus indica*	***Fabaceae***	Seed	Tamarind	Galactosyl glycerol, Procyanidin, Threo-Isocitricacid, Embelin.[18]
11	*Piper guineense*	***Piperaceae***	Seed	Ashanti Pepper	Piperine[19]
12	*Securidaca longepedunculata*	***Polygalaceae***	Root	Rhodesian violet	Chlorogenic acid.[20]
13	*Leptadenia hastate*	***Asclepiadaceae***	Leaves	Saltbush	Lupeol [21]
14	*Piper nigrum*	***Piperaceae***	Fruit	Black pepper	β-caryophyllene Piperine [22]
15	*Cola nitida*	***Malvaceae***	Bark	Kolanut	Stigmasterol [23]
16	*Allium sativum*	***Amaryllidaceae***	Bulb	Garlic	Diallyl sulfide [24]
17	*Vernonia amygdalina*	***Asteraceae***	Leaves	Bitter leaf	Caffeoylquinic acid[25]
18	*Ocimum gratissimum*	***Lamiaceae***	Leaves	Clove basil	Eugenol[26]
19	*Capsicum annuum*	***Solanaceae***	Fruits	Smallchilli pepper	Capsaicin[27]
20	*Solanum melongena*	***Solanaceae***	Fruits	Egg plant	Apigenin[28]

Table No -1- Herbal Medicinal Plant Use In Rheumatoid Arthritis

SYNTHETIC DRUGS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS:-

Rheumatoid arthritis-related joint inflammation has no cure. However, clinical studies show that when treatment with drugs known as infection altering anti-rheumatic drugs (DMARDs) begins promptly, a reduction in side effects is practically guaranteed.The types of medication that doctors recommend are based on symptoms. The following list includes the various synthetic medications used to treat rheumatoid arthritis.

1)Non-steroidal Anti-inflammatory Agents (NSAIDs):-

By lowering acute inflammation, these drugs have a potent pain-relieving and function-improving effect. All of these drugs have mild to moderate analgesic properties in addition to their modest to moderate anti-inflammatory effects. It's critical to remember that these medications don't stop joints from aging or alter the course of rheumatoid arthritis. Aspirin is the first non-steroidal medication, but due to aspirin's high rate of gastrointestinal toxicity, a narrow window between toxic and anti-inflammatory serum levels, and the inconvenience of multiple daily doses, other NSAIDs have largely replaced it as the first drug of choice for treatment. There are many NSAIDs on the market, and all of them could be equally helpful if used as directed.

The NSAIDs that are currently available have comparable toxicities. Tolerance and reaction to a specific NSAID, however, can differ greatly from person to person. Two of the many over-the-counter NSAIDS that are widely accessible are ibuprofen and naproxen. There are numerous different NSAIDS on the market; some are available without a prescription, like ibuprofen and naproxen, while many others like meloxicam and nabumetone, need one. Longer-acting NSAIDs that allow daily or twice-daily dosing may improve compliance. The COX-2 inhibitor drug class, in addition to NSAIDs, is effective at reducing inflammation. These drugs were developed to lessen the gastrointestinal risk that NSAIDS posed, but they have since been withdrawn from sale due to worries that they might increase cardiovascular risk. [29]

Mechanism of action of NSAIDS:-

By inhibiting COX-1 and COX-2 cyclooxygenase enzymes, NSAIDs stop the production of prostaglandins. Prostaglandins are essential for maintaining healthy bodily functions like vascular function, platelet stickiness, stomach acid protection, and kidney blood flow. They act as mediators of pain and inflammation. Prostaglandin production is specifically inhibited by COX-2 inhibitors; prostaglandins are key players in inflammation. [29]

Adverse effects of NSAIDS:-

The most typical NSAID side effect is gastrointestinal disturbance, which can appear clinically as burning, belching, or discomfort but actually refers to irritation of the stomach lining, erosions, and even ulcerations that may bleed. [29]

2) Corticosteroids:-

A corticosteroid with both anti-inflammatory and immunoregulatory properties is prednisone. They can be given intravenously, intramuscularly, orally, orally and intraarticularly. Corticosteroids are beneficial in the early stages of illness as a temporary adjunctive therapy while awaiting DMARDs to begin acting as an anti-inflammatory. Corticosteroids may be administered continuously as an adjunctive therapy when NSAIDs and DMARDs fall short in their ability to effectively manage a patient's severe illness. Once started, corticosteroid medication can be difficult to stop, even at low doses. For some people, tapering off of prednisone, which may be done gradually over a few weeks, can be extremely painful. [30]

Mechanism of action of corticosteroids:-

The production of Interleukin 1 (IL-1) and Tumor Necrosis Factor Alpha 1 is suppressed by corticosteroids.It has the effect of reducing joint inflammation, swelling, and pain. [30]

Adverse effect of corticosteroids:-

Corticosteroids can have a variety of side effects, including Cushing's syndrome, thinning skin, hyperglycemia, and glaucoma. Weight gain and a cushingoid appearance (increased fat deposition around the face, redness of the cheeks, and development of a "buffalo hump" over the neck) are frequent problems and the root of patient complaints. Steroid medications are associated with accelerated osteoporosis, even at a relatively low dose of 10 mg per day. [30]

3) Disease Modifying Anti-rheumatic Drugs (DMARDS):-

Both NSAIDs and DMARDs lessen the signs and symptoms of rheumatoid arthritis that is active, but only DMARDs have been shown to alter the course of the disease and improve radiological outcomes. DMARDs affect rheumatoid arthritis differently and perhaps more gradually. DMARD medications ought to typically be started as soon as rheumatoid arthritis is formally diagnosed. The presence of erosions or a narrowing of the joint space on x-rays of the affected joints is a definite indication for DMARD therapy; however, one shouldn't wait for these changes to occur. [31]

In DMARDS therapy currently using drugs are mentioned below :-

- Methotrexate
- Sulfasalazine
- Hydroxychloroquine
- Leflunomide
- Tumor Necrosis Factor Inhibitor- etanercept
- B cell depleting Agents-Rituximab
- T-cell constimulatory Blocking Agent –Abatacept
- Interleukin 1 receptor antagonist Therapy –Anakinra
- Other cytotoxic and immunomodulatory agents –Azathioprine

i.METHOTREXATE:-

Methotrexate is now regarded as the first-line DMARD drug for the majority of RA patients. At therapeutic doses, it is easily administered, has a low cost, a good toxicity profile, a relatively quick (6–8 week) onset of action, and good effectiveness. According to groups of people on various DMARDS, the majority of patients continue to take methotrexate after 5 years, a significant amount more than other treatments, demonstrating both its efficacy and tolerability. When combined with methotrexate, radiographic damage and RA symptoms can be reduced or avoided. [31]

Mechanism of action :-
The anti-inflammatory effects of methotrexate in rheumatoid arthritis appear to be connected, at least in part, to the disruption of adenosine and potential effects on other inflammatory and immunoregulatory pathways. Dihydrofolate reductase, an enzyme involved in the metabolism of folic acid, is inhibited by methotrexate, which has toxic and immunosuppressive effects. [31]

Adverse effect of Methotrexate:-
Severe myelosuppression, interstitial pneumonitis, and hepatic cirrhosis are quite rare even with adequate monitoring. Folic acid's adverse effects include GI distress, stomatitis, and oral ulcers, as well as mild alopecia, hair thinning, and modest hair loss. Supplemental folic acid may help to mitigate these adverse effects. [31]

ii. SALFASALAZINE:-
Sulfasalazine is a powerful DMARD for the treatment of RA. It has been shown to lessen signs and symptoms and postpone radiographic deterioration, despite generally being less effective than methotrexate. It is also included in a "triple therapy" regimen that has been shown to be effective for people who have not responded well to methotrexate alone, along with hydroxychloroquine and methotrexate. [32]

Mechanism of action:-
Sulfasalazine reduces inflammation by preventing prostaglandin production. Additionally, it has an impact on T-cells, which can lessen RA's autoimmune response. [32]

Adverse effect of Salfasalazine:-
Sulfasalazine may cause hypersensitivity and allergic reactions in patients who have previously experienced negative reactions to sulfa medications. Reduced frequency of mild gastrointestinal issues can be achieved through the use of enteric coated formulations or by taking the medication with meals.[32]

iii.HYDROXYCHLOROQUINE:-
Hydroxychloroquine is an antimalarial drug that is generally well-tolerated and safe for the treatment of rheumatoid arthritis. Chloroquine is an additional antimalarial medication that is occasionally used. These drugs have a limited ability to prevent joint injury on their own and should probably only be used in patients with very mild, seronegative, and nonerosive diseases. [33]

Mechanism of action:-
Antimalarial medications are used to treat rheumatoid arthritis patients, though it is unclear exactly how they work. They might change the way an antigen is presented or affect the innate immune system. [33]

Adverse effect of Hydroxychloroquine:-
Symptoms include a potentially permanent retinopathy, corneal deposits, weakened decreased accommodation (and sensitivity to light), and more. Only 1 out of every 40,000 patients who receive the recommended doses of treatment experience ocular toxicity. [33]

iv. LEFLUNOMIDE:-
Leflunomide is also a potent DMARD. Due to its effectiveness in treating signs and symptoms, it is a good alternative for those who have tried methotrexate unsuccessfully or are intolerant to it. [34]

Mechanism of action:-
Although the exact mechanism of leflunomide's action is unknown, it may be related to the drug's ability to stop the production of de novo pyrimidines by inhibiting the enzyme dihydroorotate dehydrogenase. [34]

Adverse effect of Leflunomide:-
Leflunomide's ADRs include mild gastrointestinal discomfort, alopecia, and hair thinning that might be severe enough to call for stopping the drug. Teratogenicity may also result from it. [34]

v.TUMOR NECROSIS INHIBITOR FACTOR-ENTANERCEPT:-
Lymphocytes and macrophages produce the pro-inflammatory cytokine tumor necrosis factor alpha (TNF). It is widely distributed in rheumatoid joints and is produced there by invading synovial macrophages and lymphocytes. TNF is one of the crucial cytokines that mediates joint injury and destruction due to its effects on several joint cells as well as other organs and bodily systems. [35]

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Adverse effect of Tumor Necrosis inhibitor factor:-

Upper respiratory infections, pneumonia, urinary tract infections, and skin infections are the most frequent adverse drug reactions (ADR) associated with TNF inhibitors. [35]

vi. B-CELL DEPLETING AGENTS:-

Inflammatory B cells play a number of different roles in the immune response. They perform the function of antigen-presenting cells, interact directly with T cells and other cells, can secrete cytokines, and can eventually transform into plasma cells that produce antibodies. It has been shown that B cell depletion can lessen RA signs and symptoms and slow the radiological progression of the condition. [36]

Mechanism of action:-

B cell reduction Agents are chimeric monoclonal antibodies that attach to the CD20 molecule on the surface of B cells, removing B cells from circulation as a result. [36]

Adverse effect of B-cell depleting agents:-

Hives, itching, swelling, difficulty breathing, fever, chills, and changes in blood pressure are some of the negative effects of B cell depleting agents. [36]

SL NO.	DRUG NAME	MECHANISM OF ACTION	ADVERSE EFFECT
1.	Non steroidal Anti Inflammatory Drugs (NSAID)	Prevent the production of prostaglandins by inhibiting the COX-1 and COX-2 cyclooxygenase enzymes	Gastrointestinal disturbance[29]
2.	Corticosteroids	Suppress the production of cytokines	Allergic reactions[30]
3.	Methotrexate	Disruption of adenosine and potential effects	Myelosuppression, interstitial pneumonitis[31]
4.	Salfasalazine	Inhibit the production of prostaglandins	Allergic reaction, GIT problem[32]
5.	Hydroxychloroquine	Immunomodulation	Extra ocular muscles[33]
6.	Leflunomide	Blocking the enzyme dihydroorotate dehydrogenase	GI distress, alopecia[34]
7.	Tumor Necrosis Factor Inhibitor	Blocks the excess production of TNF protein	Upper respiratory infections, pneumonia E[35]
8.	B cell depleting agents	Removal of B cells from the circulation	Hives, itching, swelling [36]

TABLE-2 – Summary of synthetic drugs use in Rheumatoid arthritis

Conclusion;

The various herbal and synthetic approaches for the treatment of rheumatoid arthritis have been covered in this paper's therapeutic section. Early diagnosis and DMARD therapy are crucial to preventing damage from occurring or becoming clinically significant. The lower the disease activity was at six months, the better the long-term prognosis; achieving rigorous clinical remission within three to six months prevents damage development irrespective of the type of therapy used. Gingerol, curcumin, and other phytochemicals have been identified as potential herbal treatments for rheumatoid arthritis.

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